

Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 354 888 A1

(12)

EUROPEAN PATENT APPLICATION
published in accordance with Art. 158(3) EPC

(43) Date of publication:
22.10.2003 Bulletin 2003/43

(21) Application number: 01994995.7

(22) Date of filing: 25.12.2001

(51) Int Cl.7: **C07H 17/02**, A61K 31/7056,
A61P 43/00, A61P 3/10,
A61P 3/04, A61P 3/06,
A61P 9/10, A61P 9/12,
A61P 9/04, A61P 19/06,
A61P 7/10

(86) International application number:
PCT/JP01/11348

(87) International publication number:
WO 02/053573 (11.07.2002 Gazette 2002/28)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: 28.12.2000 JP 2000403534

(71) Applicant: Kissei Pharmaceutical Co., Ltd.
Matsumoto-shi Nagano 399-8710 (JP)

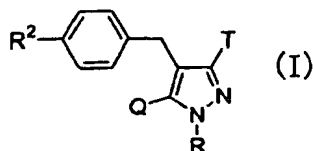
(72) Inventors:
• FUJIKURA, Hideki
Matsumoto-shi, Nagano 390-0851 (JP)

• FUSHIMI, Nobuhiko
Matsumoto-shi, Nagano 390-0313 (JP)
• NISHIMURA, Toshihiro
Minamiazumi-gun, Nagano 399-8304 (JP)
• NAKABAYASHI, Takeshi
Matsumoto-shi, Nagano 390-0312 (JP)
• ISAJI, Masayuki
Shiojiri-shi, Nagano 399-0704 (JP)

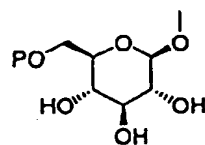
(74) Representative: Hayes, Adrian Chetwynd et al
Boulton Wade Tennant,
Verulam Gardens
70 Gray's Inn Road
London WC1X 8BT (GB)

(54) **GLUCOPYRANOSYLOXYPYRAZOLE DERIVATIVES AND USE THEREOF IN MEDICINES**

(57) The present invention provides glucopyranosyloxy-pyrazole derivatives represented by the general formula:



wherein R represents a hydrogen atom, a lower alkyl group or a group forming a prodrug; one of Q and T represents a group represented by the general formula:



(wherein P represents a hydrogen atom or a group forming a prodrug), while the other represents a lower alkyl group or a halo(lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or pharmaceutically acceptable salts thereof, which exert an inhibitory activity in human SGLT2 and have an improved oral absorption, and therefore are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications or obesity, and pharmaceutically acceptable salts thereof, and pharmaceutical uses thereof.

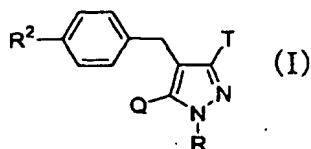
EP 1 354 888 A1

Description

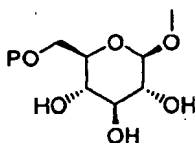
Technical Field

[0001] The present invention relates to glucopyranosyloxypyrazole derivatives or pharmaceutically acceptable salts thereof which are useful as medicaments and pharmaceutical uses thereof.

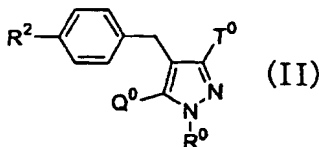
[0002] More particularly, the present invention relates to glucopyranosyloxypyrazole derivatives represented by the general formula:



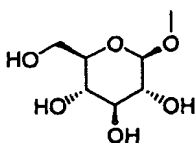
wherein R represents a hydrogen atom, a lower alkyl group or a group forming a prodrug; one of Q and T represents a group represented by the general formula:



(wherein P represents a hydrogen atom or a group forming a prodrug), while the other represents a lower alkyl group or a halo(lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or pharmaceutically acceptable salts thereof, which are useful as agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications or obesity, of which glucopyranosyloxypyrazole derivatives, which have an inhibitory activity in human SGLT2, represented by the general formula:



wherein R⁰ represents a hydrogen atom or a lower alkyl group; one of Q⁰ and T⁰ represents a group represented by the general formula:



while the other represents a lower alkyl group or a halo(lower alkyl) group; and R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom, are active forms, and to pharmaceutical uses thereof.

Background Art

[0003] Diabetes is a lifestyle-related disease with the background of change of eating habit and lack of exercise. Hence, diet and exercise therapies are performed in patients with diabetes. Furthermore, when its sufficient control and continuous therapies are difficult, drug treatment is simultaneously performed. Now, biguanides, sulfonylureas and insulin sensitivity enhancers have been employed as antidiabetic agents. However, biguanides and sulfonylureas show occasionally adverse effects such as lactic acidosis and hypoglycemia, respectively. In a case of using insulin sensitivity enhancers, adverse effects such as edema are occasionally observed, and it is also implicated in advancing obesity. Therefore, in order to solve these problems, it has been desired to develop antidiabetic agents having a new mechanism.

[0004] In recent years, development of new type antidiabetic agents has been progressing, which promote urinary glucose excretion and lower blood glucose level by preventing excess glucose reabsorption at the kidney (J. Clin. Invest., Vol.79, pp.1510-1515 (1987)). In addition, it is reported that SGLT2 (Na⁺/glucose cotransporter 2) is present in the S1 segment of the kidney's proximal tubule and participates mainly in reabsorption of glucose filtrated through glomerular (J. Clin. Invest., Vol.93, pp.397-404 (1994)). Accordingly, inhibiting a human SGLT2 activity prevents reabsorption of excess glucose at the kidney, subsequently promotes excreting excess glucose through the urine, and normalizes blood glucose level. Therefore, fast development of antidiabetic agents, which have a potent inhibitory activity in human SGLT2 and have a new mechanism, has been desired. Also, since such agents promote the excretion of excess glucose through the urine and consequently the glucose accumulation in the body is decreased, they are also expected to have a preventing or alleviating effect on obesity and a urinating effect. Furthermore, the agents are considered to be useful for various related diseases which occur accompanying the progress of diabetes or obesity due to hyperglycemia.

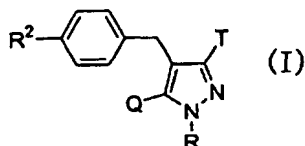
[0005] As compounds having pyrazole moiety, it is described that WAY-123783 increased an amount of excreted glucose in normal mice. However, its effects in human are not described at all (J. Med. Chem., Vol. 39, pp. 3920-3928 (1996)).

Disclosure of the Invention

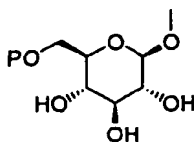
[0006] The present inventors have studied earnestly to find compounds having an inhibitory activity in human SGLT2. As a result, it was found that compounds represented by the above general formula (I) are converted into glucopyranosyloxypyrazole derivatives represented by the above general formula (II) as their active forms *in vivo*, and show an excellent inhibitory activity in human SGLT2 as mentioned below, thereby forming the basis of the present invention.

[0007] The present invention is to provide the following glucopyranosyloxypyrazole derivatives or pharmaceutically acceptable salts thereof, which exert an inhibitory activity in human SGLT2 *in vivo* and show an excellent hypoglycemic effect by excreting excess glucose in the urine through preventing the reabsorption of glucose at the kidney, and to provide pharmaceutical uses thereof.

[0008] Thus, the present invention relates to a glucopyranosyloxypyrazole derivative represented by the general formula:



wherein R represents a hydrogen atom, a lower alkyl group or a group forming a prodrug; one of Q and T represents a group represented by the general formula:



(wherein P represents a hydrogen atom or a group forming a prodrug), while the other represents a lower alkyl group

or a halo(lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

[0009] Also, the present invention relates to a pharmaceutical composition, a human SGLT2 inhibitor and an agent for the prevention or treatment of a disease associated with hyperglycemia, which comprises as an active ingredient a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

[0010] The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof.

[0011] The present invention relates to a use of a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

[0012] Furthermore, the present invention relates to a pharmaceutical combination which comprises (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, proboccol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer.

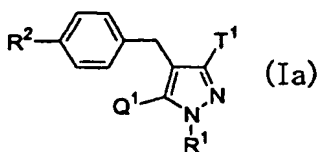
[0013] The present invention relates to a method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, in combination with (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, proboccol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting

antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer.

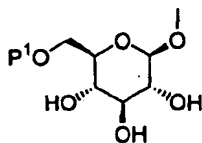
[0014] The present invention relates to a use of (A) a glucopyranosyloxypyrazole derivative represented by the above general formula (I) or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probucol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxigenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

[0015] In the present invention, the term "prodrug" means a compound which is converted into a glucopyranosyloxypyrazole derivative represented by the above general formula (II) as an active form thereof *in vivo*. As examples of groups forming prodrugs, in cases of such groups located at a hydroxy group, a hydroxy-protective group used generally as a prodrug such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group and a lower alkoxy-substituted (lower alkoxycarbonyl) group are illustrated, and in cases of such groups located at a nitrogen atom, an amino-protective group used generally as a prodrug such as a lower acyl group, a lower alkoxycarbonyl group, a lower acyloxymethyl group and a lower alkoxycarbonyloxymethyl group are illustrated.

[0016] As the glucopyranosyloxypyrazole derivatives represented by the above general formula (I), for example, compounds represented by the general formula:



wherein R^1 represents a hydrogen atom, a lower alkyl group, a lower acyl group, a lower alkoxycarbonyl group, a lower acyloxymethyl group or a lower alkoxycarbonyloxymethyl group; one of Q^1 and T^1 represents a group represented by the general formula:



(wherein P^1 represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower

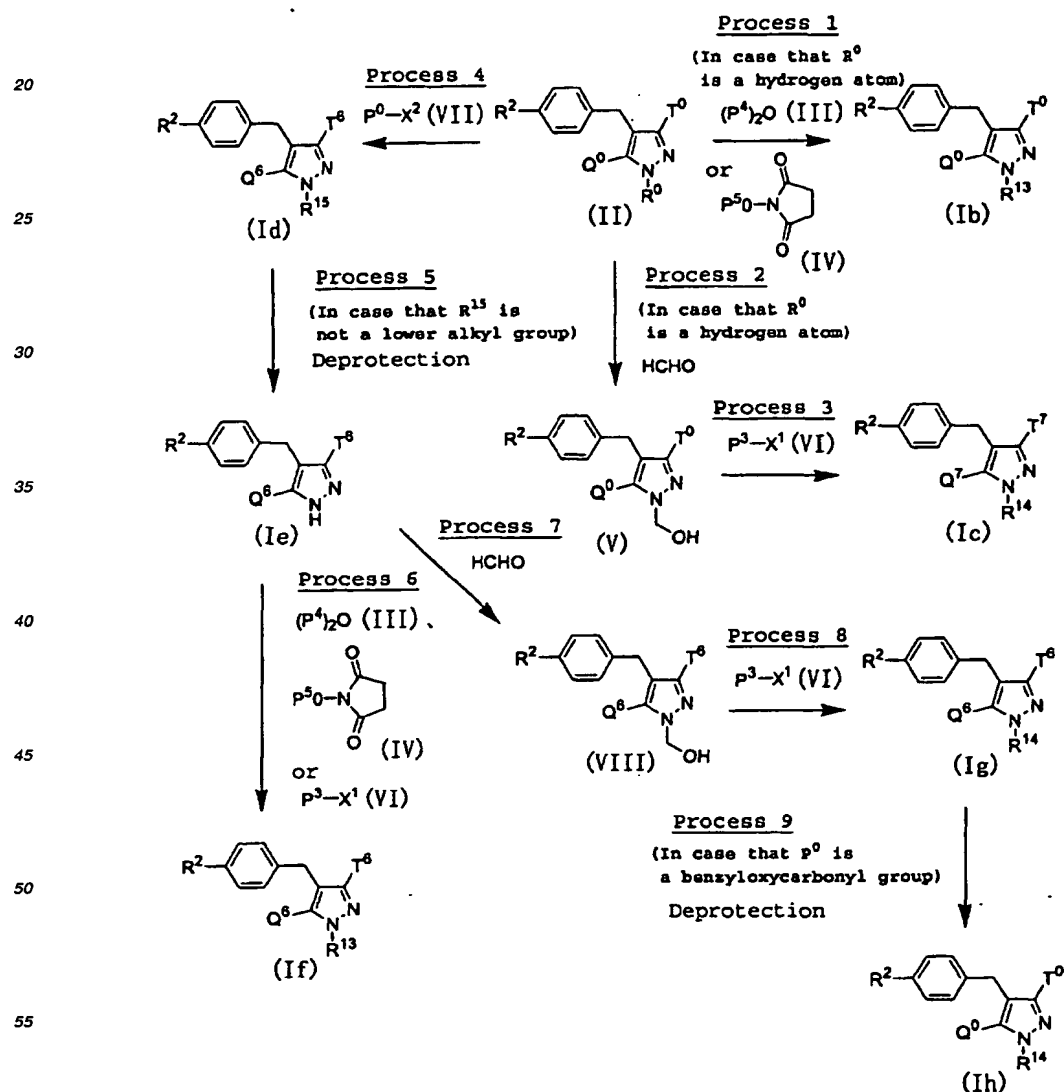
[0018] In the substituent R, a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms are preferable; a hydrogen atom, an ethyl group, a propyl group or an isopropyl group are more preferable; and an isopropyl group is most preferable because of metabolic stability in human liver S9 fraction. In the substituent R², a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms, or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms are preferable; and an ethyl group, an ethoxy group, an isopropoxy group, a methoxy group or a methylthio group are more preferable. In the substituents Q and T, it is preferable that the substituent Q is a lower alkyl group or a halo(lower alkyl) group. Among them, a lower alkyl group is preferable; a straight-chained or branched alkyl group having 1 to 3 carbon atoms is more preferable; and a methyl group is most preferable. In the substituent P, a lower acyl group and a lower alkoxycarbonyl group are preferable; a lower alkoxycarbonyl group is more preferable; and a straight-chained or branched alkoxycarbonyl group having 2 to 5 carbon atoms is most preferable. Concretely, a methoxycarbonyl group, an ethoxycarbonyl group, an isopropoxycarbonyl group or an isobutoxycarbonyl group are preferable.

6.

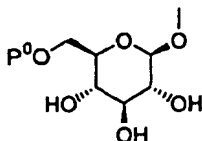
propyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole, 3-(6-O-isopropoxycarbonyl-β-D-glucopyranosyloxy)-1-isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole, 3-(6-O-isobutoxycarbonyl-β-D-glucopyranosyloxy)-1-isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole and the like are preferable; 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxycarbonyl-β-D-glucopyranosyloxy)-5-methylpyrazole, 3-(6-O-ethoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole, 3-(6-O-isopropoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole, 3-(6-O-isobutoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole and the like are more preferable; and 3-(6-O-ethoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole and the like are most preferable.

[0020] The compounds represented by the above general formula (I) of the present invention can be prepared by introducing hydroxy- and/or amino-protective groups capable of using generally as a prodrug into a hydroxy group and/or a nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) in usual way.

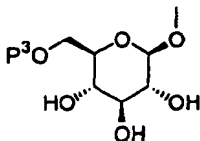
[0021] For example, the compounds of the present invention can be prepared using a glucopyranosyloxypyrazole derivative represented by the above general formula (II) according to the following procedure or analogous procedures thereof:



Wherein P^0 represents a hydroxy-protective group such as a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group, a lower alkoxy-substituted (lower alkoxy-carbonyl) group or a benzyloxy-carbonyl group; P^3 represents a lower acyl group or a lower alkoxy-carbonyl group; P^4 represents a lower acyl group; P^5 represents a lower alkoxy-carbonyl group; R^{13} represents a lower acyl group or a lower alkoxy-carbonyl group; R^{14} represents a lower acyloxymethyl group or a lower alkoxy-carbonyloxymethyl group; R^{15} represents an amino-protective group such as a lower alkyl group, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group, a lower alkoxy-substituted (lower alkoxy-carbonyl) group or a benzyloxy-carbonyl group; one of Q^6 and T^6 represents a group represented by the general formula:



(wherein P^0 has the same meaning as defined above), while the other represents a lower alkyl group or a halo(lower alkyl) group; one of Q^7 and T^7 represents a group represented by the general formula:



(wherein P^3 has the same meaning as defined above), while the other represents a lower alkyl group or a halo (lower alkyl) group; X^1 and X^2 represent a leaving group such as a bromine atom or a chlorine atom; and R^0 , R^2 , Q^0 and T^0 have the same meanings as defined above.

Process 1

[0022] A prodrug represented by the above general formula (Ib) can be prepared by protecting the nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) with an aliphatic acid anhydride represented by the above general formula (III) in an aliphatic acid such as acetic acid at usually 0°C to reflux temperature for usually 30 minutes to 1 day, or alternatively, by protecting the nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) with a succinimide derivative represented by the above general formula (IV) in an inert solvent such as tetrahydrofuran at usually room temperature to reflux temperature for usually 1 hour to 1 day. The reaction time can be appropriately varied based on starting material used, solvent and reaction temperature.

Process 2

[0023] A compound represented by the above general formula (V) can be prepared by introducing a hydroxymethyl group into the nitrogen atom of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) using formaldehyde in a solvent. As the solvent used in the reaction, water, methanol, ethanol, tetrahydrofuran, dichloromethane, ethyl acetate, *N,N*-dimethylformamide, acetonitrile, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

Process 3

[0024] A prodrug represented by the above general formula (Ic) can be prepared by protecting the hydroxymethyl group of a compound represented by the above general formula (V) with a reagent for protecting represented by the above general formula (VI) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, pi-

coline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on starting material used, solvent and reaction temperature.

Process 4

[0025] A prodrug represented by the above general formula (Id) or an analogous compound thereof can be prepared by protecting the hydroxymethyl group, or the nitrogen atom and the hydroxymethyl group of a glucopyranosyloxypyrazole derivative represented by the above general formula (II) with a reagent for protecting represented by the above general formula (VII) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on starting material used, solvent and reaction temperature.

Process 5

[0026] A prodrug represented by the above general formula (Ie) or an analogous compound thereof can be prepared by subjecting a compound represented by the above general formula (Id) to deacylation in the presence of a weak base such as sodium hydrogen carbonate, sodium carbonate or potassium carbonate in an alcoholic solvent such as methanol or ethanol. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 15 minutes to 1 day, varying based on starting material used, solvent and reaction temperature. Process 6

[0027] A prodrug represented by the above general formula (If) or an analogous compound thereof can be prepared by protecting the nitrogen atom of a compound represented by the above general formula (Ie) with an aliphatic acid anhydride represented by the above general formula (III) in an aliphatic acid such as acetic acid at usually 0°C to reflux temperature for usually 30 minutes to 1 day, alternatively, with a succinimide derivative represented by the above general formula (IV) in an inert solvent such as tetrahydrofuran at usually room temperature to reflux temperature for 1 hour to 1 day, and further alternatively, with a reagent for protecting represented by the above general formula (VI) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent such as dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol or a mixed solvent thereof, or without any solvent at usually -40°C to reflux temperature for 30 minutes to 2 days. The reaction time can be appropriately varied based on starting material used, solvent and reaction temperature.

Process 7

[0028] A compound represented by the above general formula (VIII) can be prepared by introducing a hydroxymethyl group into the nitrogen atom of a compound represented by the above general formula (Ie) using formaldehyde in a various solvent. As the solvent used in the reaction, water, methanol, ethanol, tetrahydrofuran, dichloromethane, ethyl acetate, *N,N*-dimethyl-formamide, acetonitrile, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

Process 8

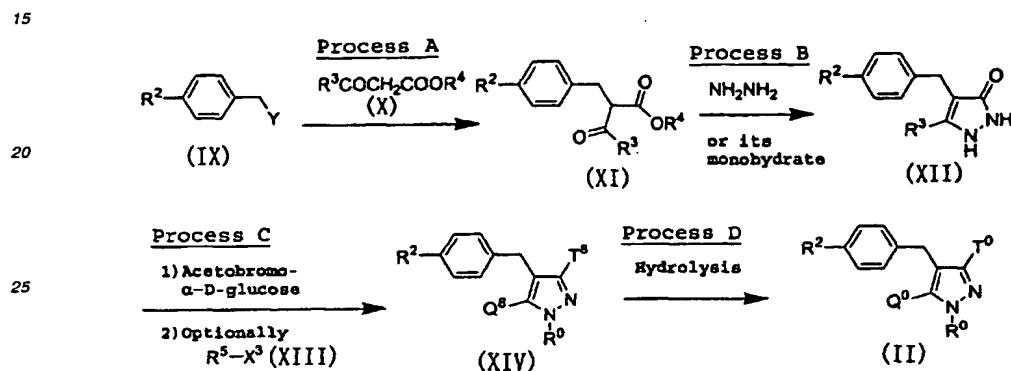
[0029] A prodrug represented by the above general formula (Ig) or an analogous compound thereof can be prepared by protecting the hydroxymethyl group of a compound represented by the above general formula (VIII) with a reagent for protecting represented by the above general formula (VI) in the presence of a base such as pyridine, triethylamine, *N,N*-diisopropylethylamine, picoline, lutidine, collidine, quinuclidine, 1,2,2,6,6-pentamethylpiperidine or 1,4-diazabicyclo[2.2.2]octane in an inert solvent or without any solvent. As the inert solvent used in the reaction, dichloromethane, acetonitrile, ethyl acetate, diisopropyl ether, chloroform, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, acetone, *tert*-butanol, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from -40°C to reflux temperature, and the reaction time is usually from 30 minutes to 2 days, varying based on starting material used,

solvent and reaction temperature.

Process 9

[0030] A prodrug represented by the above general formula (Ih) can be prepared by subjecting a compound represented by the above general formula (Ig) to deprotection by catalytic hydrogenation in the presence of a palladium catalyst such as palladium carbon in an inert solvent. As the inert solvent used in the reaction, methanol, ethanol, tetrahydrofuran, ethyl acetate, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from 0°C to reflux temperature, and the reaction time is usually from 30 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

[0031] For example, the compounds represented by the above general formula (II) which are used as starting materials in the aforementioned production process can be prepared according to the following procedure:



wherein X^3 and Y represent a leaving group such as a halogen atom, a mesyloxy group or a tosyloxy group; R^3 represents a lower alkyl group or a halo (lower alkyl) group; R^4 represents a methyl group or an ethyl group; R^5 represents a lower alkyl group; one of Q^8 and T^8 represents a 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyloxy group, while the other represents a lower alkyl group or a halo(lower alkyl) group; and R^0 , R^2 , Q^0 and T^0 have the same meanings as defined above.

Process A

[0032] A compound represented by the above general formula (XI) can be prepared by condensing a benzyl derivative represented by the above general formula (IX) with a ketoacetate represented by the above general formula (X) in the presence of a base such as sodium hydride or potassium tert-butoxide in an inert solvent. As the inert solvent used in the reaction, 1, 2-dimethoxyethane, tetrahydrofuran, *N,N*-dimethylformamide, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature.

Process B

[0033] A pyrazolone derivative represented by the above general formula (XII) can be prepared by condensing a compound represented by the above general formula (XI) with hydrazine or hydrazine monohydrate in an inert solvent. As the inert solvent used in the reaction, toluene, tetrahydrofuran, chloroform, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature. The obtained pyrazolone derivative represented by the above general formula (XII) can be also used in process C after converting into a salt thereof in usual way.

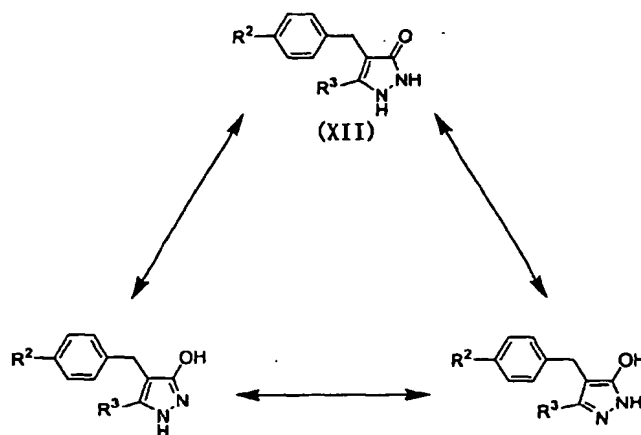
Process C

[0034] In case of pyrazolone derivatives represented by the above general formula (XII) wherein R^3 is a lower alkyl group, a corresponding compound represented by the above general formula (XIV) can be prepared by subjecting a

corresponding pyrazolone derivative represented by the above general formula (XII) to glycosidation using acetobromo- α -D-glucose in the presence of a base such as silver carbonate in an inert solvent, and subjecting the resulting compound to *N*-alkylation using an alkylating agent represented by the above general formula (XIII) in the presence of a base such as potassium carbonate in an inert solvent as occasion demands. As the solvent used in the glycosidation reaction, tetrahydrofuran and the like are illustrations. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature. As the solvent used in the *N*-alkylation reaction, acetonitrile, *N,N*-dimethylformamide, tetrahydrofuran, a mixed solvent thereof and the like can be illustrated. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature.

[0035] In case of pyrazolone derivatives represented by the above general formula (XII) wherein R^3 is a halo(lower alkyl) group, a corresponding compound represented by the above general formula (XIV) can be prepared by subjecting a corresponding pyrazolone derivative represented by the above general formula (XII) to glycosidation using acetobromo- α -D-glucose in the presence of a base such as potassium carbonate in an inert solvent, and subjecting the resulting compound to *N*-alkylation using an alkylating agent represented by the above general formula (XIII) in the presence of a base such as potassium carbonate in an inert solvent as occasion demands. As the solvent used in the glycosidation reaction, acetonitrile, tetrahydrofuran and the like are illustrations. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature. As the solvent used in the *N*-alkylation reaction, acetonitrile, *N,N*-dimethylformamide, tetrahydrofuran, a mixed solvent thereof and the like are illustrations. The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 1 hour to 1 day, varying based on starting material used, solvent and reaction temperature.

[0036] In the compound represented by the above general formula (XII) as starting materials, there are the following three tautomers, varying based on the change of reaction conditions:



wherein R^2 and R^3 have the same meanings as defined above.

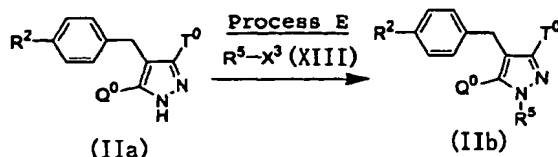
[0037] The obtained compounds represented by the above general formula (XIV) can be also used in process D after converting into a salt thereof in usual way.

Process D

[0038] A glucopyranosyloxypyrazole represented by the above general formula (II) can be prepared by subjecting a compound represented by the above general formula (XIV) to hydrolysis. As the solvent used in the reaction, methanol, ethanol, tetrahydrofuran, water, a mixed solvent thereof and the like are illustrations, and as the base used, sodium hydroxide, sodium ethoxide and the like are illustrations. The reaction temperature is usually from 0°C to room temperature, and the reaction time is usually from 30 minutes to 6 hours, varying based on starting material used, solvent and reaction temperature.

[0039] Of the compounds represented by the above general formula (II) which are also used as starting materials in the aforementioned production process, compounds wherein the substituent R^0 is a lower alkyl group can be also

prepared according to the following procedure:



10 wherein R², R⁵, Q⁰, T⁰ and X³ have the same meanings as defined above.

Process E

15 [0040] A compound represented by the above general formula (IIb) can be prepared by subjecting a compound represented by the above general formula (IIa) to *N*-alkylation using an *N*-alkylating agent represented by the above general formula (XIII) in the presence of a base such as potassium carbonate or cesium carbonate, and occasionally a catalytic amount of sodium iodide in an inert solvent. As the inert solvent used in the reaction, *N,N*-dimethylformamide, 1,2-dimethoxyethane, dimethyl sulfoxide, tetrahydrofuran, ethanol, a mixed solvent thereof and the like are illustrations.

20 The reaction temperature is usually from room temperature to reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on starting material used, solvent and reaction temperature.

[0041] The compounds represented by the above general formula (I) of the present invention obtained by the above production processes can be isolated and purified by conventional separation means such as fractional recrystallization, purification using chromatography, solvent extraction and solid phase extraction.

25 [0042] The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention can be converted into their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, acid addition salts with organic acids such as formic acid, acetic acid, methanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, glutamic acid, aspartic acid, adipic acid, oleic acid, stearic acid and the like, and salts with inorganic bases such as a sodium salt, a potassium salt, a calcium salt, a magnesium salt and the like.

[0043] The prodrugs represented by the above general formula (I) of the present invention include their solvates with pharmaceutically acceptable solvents such as ethanol and water.

35 [0044] Of the compounds represented by the above general formula (I) of the present invention, there are two optical isomers, *R*-isomer and *S*-isomer, in each compound having an asymmetric carbon atom excluding the glucopyranosyloxy moiety. In the present invention, either of *R*-isomer or *S*-isomer can be employed, and a mixture of both isomers can be also employed.

40 [0045] The prodrugs represented by the above general formula (I) of the present invention are converted into glucopyranosyloxypyrazole derivatives represented by the above general formula (II) as their active forms *in vivo*, and show an excellent inhibitory activity in human SGLT2. On the other hand, since WAY-123783 has an extremely weak inhibitory activity in human SGLT2, it can not be expected that it exerts a sufficient effect as a human SGLT2 inhibitor. In addition, the prodrugs represented by the above general formula (I) of the present invention have an improved oral absorption, and pharmaceutical compositions comprising the prodrug as an active ingredient are highly useful as oral formulations. Therefore, the prodrugs of the present invention are extremely useful as agents for the prevention or

45 treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications (e.g., retinopathy, neuropathy, nephropathy, ulcer, macroangiopathy), obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia, gout or the like.

50 [0046] Furthermore, the compounds of the present invention can be suitably used in combination with at least one member selected from drugs other than SGLT2 inhibitors. Examples of the drugs which can be used in combination with the compounds of the present invention include an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation

inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor (PDGF), a platelet-derived growth factor (PDGF) analogue (e.g., PDGF-AA, PDGF-BB, PDGF-AB), epidermal growth factor (EGF), nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, proboccol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyltransferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.

[0047] In case of uses of the compound of the present invention in combination with the above one or more drugs, the present invention includes either dosage forms of simultaneous administration as a single preparation or separated preparations by the same or different administration routes, and administration at different dosage intervals as separated preparations by the same or different administration routes. A pharmaceutical combination comprising the compound of the present invention and the above one or more drugs includes both dosage forms as a single preparation and separated preparations for combination as mentioned above.

[0048] The compounds of the present invention can achieve more advantageous effects than additive effects in the prevention or treatment of the above diseases when used suitably in combination with the above drugs. Also, the administration dose can be decreased in comparison with administration of either drug alone, or adverse effects of coadministered drugs other than SGLT2 inhibitors can be avoided or reduced.

[0049] Specific compounds as the above drugs used in combination and preferable diseases to be treated are exemplified as follows. However, the present invention is not limited thereto, and for example, the specific compounds include their free compounds, and their or other pharmaceutically acceptable salts.

[0050] As insulin sensitivity enhancers, peroxisome proliferator-activated receptor- γ agonists such as troglitazone, pioglitazone hydrochloride, rosiglitazone maleate, sodium darglitazone, GI-262570, isaglitazone, LG-100641, NC-2100, T-174, DRF-2189, CLX-0921, CS-011, GW-1929, ciglitazone, sodium englitazone and NIP-221, peroxisome proliferator-activated receptor- α agonists such as GW-9578 and BM-170744, peroxisome proliferator-activated receptor- α/γ agonists such as GW-409544, KRP-297, NN-622, CLX-0940, LR-90, SB-219994, DRF-4158 and DRF-MDX8, retinoid X receptor agonists such as ALRT-268, AGN-4204, MX-6054, AGN-194204, LG-100754 and bexarotene, and other insulin sensitivity enhancers such as reglinox, ONO-5816, MBX-102, CRE-1625, FK-614, CLX-0901, CRE-1633, NN-2344, BM-13125, BM-501050, HQL-975, CLX-0900, MBX-668, MBX-675, S-15261, GW-544, AZ-242, LY-510929, AR-H049020 and GW-501516 are illustrated. Insulin sensitivity enhancers are used preferably for diabetes, diabetic complications, obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for diabetes, hyperinsulinemia or glucose metabolism disorder because of improving the disturbance of insulin signal transduction in peripheral tissues and enhancing glucose uptake into the tissues from the blood, leading to lowering of blood glucose level.

[0051] As glucose absorption inhibitors, α -glucosidase inhibitors such as acarbose, voglibose, miglitol, CKD-711, emiglitate, MDL-25,637, camiglibose and MDL-73,945, and α -amylase inhibitors such as AZM-127 are illustrated. Glucose absorption inhibitors are used preferably for diabetes, diabetic complications, obesity, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder because of inhibiting the gastrointestinal enzymatic digestion of carbohydrates contained in foods, and inhibiting or delaying the absorption of glucose into the body.

[0052] As biguanides, phenformin, buformin hydrochloride, metformin hydrochloride or the like are illustrations. Biguanides are used preferably for diabetes, diabetic complications, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes, hyperinsulinemia or glucose metabolism disorder because of lowering blood glucose level by inhibitory effects on hepatic gluconeogenesis, accelerating effects on anaerobic glycolysis in tissues or improving effects on insulin resistance in peripheral tissues.

[0053] As insulin secretion enhancers, tolbutamide, chlor-propamide, tolazamide, acetohexamide, glycopyramide, glyburide (glibenclamide), gliclazide, 1-butyl-3-metaniyl-urea, carbutamide, glibomuride, glipizide, gliquidone, glisoxapide, glybuthiazol, glybuzole, sodium glymidine, glypinamide, phenbutamide, tolcyclamide, glimepiride, nateglinide, mitigliidine calcium hydrate, repaglinide or the like are illustrations. Insulin secretion enhancers are used preferably for diabetes, diabetic complications or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder because of lowering blood glucose level by acting on pancreatic β -cells and enhancing the insulin secretion.

[0054] As insulin preparations, human insulin, human insulin analogues, animal-deprived insulin or the like are illustrations. Insulin preparations are used preferably for diabetes, diabetic complications or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder.

[0055] As glucagon receptor antagonists, BAY-27-9955, NNC-92-1687 or the like are illustrations; as insulin receptor kinase stimulants, TER-17411, L-783281, KRX-613 or the like are illustrations; as tripeptidyl peptidase II inhibitors, UCL-1397 or the like are illustrations; as dipeptidyl peptidase IV inhibitors, NVP-DPP728A, TSL-225, P-32/98 or the like are illustrations; as protein tyrosine phosphatase 1B inhibitors, PTP-112, OC-86839, PNU-177496 or the like are illustrations; as glycogen phosphorylase inhibitors, NN-4201, CP-368296 or the like are illustrations; as fructose-bisphosphatase inhibitors, R-132917 or the like are illustrations; as pyruvate dehydrogenase inhibitors, AZD-7545 or the like are illustrations; as hepatic gluconeogenesis inhibitors, FR-225659 or the like are illustrations; as glucagon-like peptide-1 analogues, exendin-4, CJC-1131 or the like are illustrations; as glucagon-like peptide 1 agonists; AZM-134, LY-315902 or the like are illustrations; and as amylin, amylin analogues or amylin agonists, pramlintide acetate or the like are illustrations. These drugs, glucose-6-phosphatase inhibitors, D-chiroinositol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1 are used preferably for diabetes, diabetic complications, hyperinsulinemia or glucose metabolism disorder, and more preferably for diabetes or glucose metabolism disorder.

[0056] As aldose reductase inhibitors, ascorbyl gamolenate, tolrestat, epalrestat, ADN-138, BAL-ARI8, ZD-5522, ADN-311, GP-1447, IDD-598, fidarestat, sorbinil, ponalrestat, risarestat, zenarestat, minalrestat, methosorbinil, AL-1567, imirestat, M-16209, TAT, AD-5467, zopolrestat, AS-3201, NZ-314, SG-210, JTT-811, lindolrestat or the like are illustrations. Aldose reductase inhibitors are preferably used for diabetic complications because of inhibiting aldose reductase and lowering excessive intracellular accumulation of sorbitol in accelerated polyol pathway which are in continuous hyperglycemic condition in the tissues in diabetic complications.

[0057] As advanced glycation endproduct formation inhibitors, pyridoxamine, OPB-9195, ALT-946, ALT-711, pimagedine hydrochloride or the like are illustrations. Advanced glycation endproduct formation inhibitors are preferably used for diabetic complications because of inhibiting formation of advanced glycation endproducts which is accelerated in continuous hyperglycemic condition in diabetes and reduction of cellular damage.

[0058] As protein kinase C inhibitors, LY-333531, midostaurin or the like are illustrations. Protein kinase C inhibitors are preferably used for diabetic complications because of inhibiting of protein kinase C activity which is accelerated in continuous hyperglycemic condition in diabetes.

[0059] As γ -aminobutyric acid receptor antagonists, topiramate or the like are illustrations; as sodium channel antagonists, mexiletine hydrochloride, oxcarbazepine or the like are illustrations; as transcript factor NF- κ B inhibitors, dexlipotam or the like are illustrations; as lipid peroxidase inhibitors, tirilazad mesylate or the like are illustrations; as *N*-acetylated- α -linked-acid-dipeptidase inhibitors, GPI-5693 or the like are illustrations; and as carnitine derivatives, carnitine, levacecarnine hydrochloride, levocarnitine chloride, levocarnitine, ST-261 or the like are illustrations. These drugs, insulin-like growth factor-I, platelet-derived growth factor, platelet derived growth factor analogues, epidermal growth factor, nerve growth factor, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimocloamol, sulodexide and Y-128 are preferably used for diabetic complications.

[0060] As hydroxymethylglutaryl coenzyme A reductase inhibitors, sodium cerivastatin, sodium pravastatin, lovastatin, simvastatin, sodium fluvastatin, atorvastatin calcium hydrate, SC-45355, SQ-33600, CP-83101, BB-476, L-669262, S-2468, DMP-565, U-20685, BAY-x-2678, BAY-10-2987, calcium pitavastatin, calcium rosuvastatin, colestolone, dalvastatin, acitemate, mevastatin, crilvastatin, BMS-180431, BMY-219501 glenvastatin, carvastatin, BMY-22089, bervastatin or the like are illustrations. Hydroxymethylglutaryl coenzyme A reductase inhibitors are used preferably for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypercholesterolemia or atherosclerosis because of lowering blood cholesterol level by inhibiting hydroxymethylglutaryl coenzyme A reductase.

[0061] As fibric acid derivatives, bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, aluminum clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, AHL-157 or the like are illustrated. Fibric acid derivatives are used preferably for hyper-insulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder or atherosclerosis, and more preferably for hyperlipidemia, hypertriglyceridemia or atherosclerosis because of activating hepatic lipoprotein lipase and enhancing fatty acid oxidation, leading to lowering of blood triglyceride level.

[0062] As β_3 -adrenoceptor agonists, BRL-28410, SR-58611A, ICI-198157, ZD-2079, BMS-194449, BRL-37344, CP-331679, CP-114271, L-750355, BMS-187413, SR-59062A, BMS-210285, LY-377604, SWR-0342SA, AZ-40140, SB-226552, D-7114, BRL-35135, FR-149175, BRL-26830A, CL-316243, AJ-9677, GW-427353, N-5984, GW-2696 or the like are illustrations. β_3 -Adrenoceptor agonists are used preferably for obesity, hyperinsulinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder, and more preferably for obesity or hyperinsulinemia because of stimulating β_3 -adrenoceptor in adipose tissue and enhancing the fatty acid oxidation, leading to induction of energy expenditure.

[0063] As acyl-coenzyme A cholesterol acyltransferase inhibitors, NTE-122, MCC-147, PD-132301-2, DUP-129, U-

73482, U-76807, RP-70676, P-06139, CP-113818, RP-73163, FR-129169, FY-038, EAB-309, KY-455, LS-3115, FR-145237, T-2591, J-104127, R-755, FCE-28654, YIC-C8-434, avasimibe, CI-976, RP-64477, F-1394, eldacinibe, CS-505, CL-283546, YM-17E, lecinibide, 447C88, YM-750, E-5324, KW-3033, HL-004, eflocimibe or the like are illustrations. Acyl-coenzyme A cholesterol acyltransferase inhibitors are used preferably for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder, and more preferably for hyperlipidemia or hypercholesterolemia because of lowering blood cholesterol level by inhibiting acyl-coenzyme A cholesterol acyltransferase.

[0064] As thyroid hormone receptor agonists, sodium liothyronine, sodium levothyroxine, KB-2611 or the like are illustrations; as cholesterol absorption inhibitors, ezetimibe, SCH-48461 or the like are illustrations; as lipase inhibitors, orlistat, ATL-962, AZM-131, RED-103004 or the like are illustrations; as carnitine palmitoyltransferase inhibitors, etomoxir or the like are illustrations; as squalene synthase inhibitors, SDZ-268-198, BMS-188494, A-87049, RPR-101821, ZD-9720, RPR-107393, ER-27856 or the like are illustrations; as nicotinic acid derivatives, nicotinic acid, nicotinamide, nicomol, niceritrol, acipimox, nicorandil or the like are illustrations; as bile acid sequestrants, colestyramine, colestilan, colesevelam hydrochloride, GT-102-279 or the like are illustrations; as sodium/bile acid cotransporter inhibitors, 264W94, S-8921, SD-5613 or the like are illustrations; and as cholesterol ester transfer protein inhibitors, PNU-107368E, SC-795, JTT-705, CP-529414 or the like are illustrations. These drugs, probocel, microsomal triglyceride transfer protein inhibitors, lipoxigenase inhibitors and low-density lipoprotein receptor enhancers are preferably used for hyperlipidemia, hypercholesterolemia, hypertriglyceridemia or lipid metabolism disorder.

[0065] As appetite suppressants, monoamine reuptake inhibitors, serotonin reuptake inhibitors, serotonin releasing stimulants, serotonin agonists (especially 5HT_{2C}-agonists), noradrenaline reuptake inhibitors, noradrenaline releasing stimulants, α_1 -adrenoceptor agonists, β_2 -adrenoceptor agonists, dopamine agonists, cannabinoid receptor antagonists, γ -aminobutyric acid receptor antagonists, H₃-histamine antagonists, L-histidine, leptin, leptin analogues, leptin receptor agonists, melanocortin receptor agonists (especially MC3-R agonists, MC4-R agonists) α -melanocyte stimulating hormone, cocaine and amphetamine-regulated transcript, mahogany protein, enterostatin agonists, calcitonin, calcitonin-gene-related peptide, bombesin, cholecystokinin agonists (especially CCK-A agonists), corticotropin-releasing hormone, corticotrophin-releasing hormone analogues, corticotropin-releasing hormone agonists, urocortin, somatostatin, somatostatin analogues, somatostatin receptor agonists, pituitary adenylate cyclase-activating peptide, brain-derived neurotrophic factor, ciliary neurotrophic factor, thyrotropin-releasing hormone, neurotensin, sauvagine, neuropeptide Y antagonists, opioid peptide antagonists, galanin antagonists, melanin-concentrating hormone antagonists, agouti-related protein inhibitors and orexin receptor antagonists are illustrations. Specifically, as monoamine reuptake inhibitors, mazindol or the like are illustrations; as serotonin reuptake inhibitors, dexfenfluramine hydrochloride, fenfluramine, sibutramine hydrochloride, fluvoxamine maleate, sertraline hydrochloride or the like are illustrations; as serotonin agonists, inotriptan, (+)-norfenfluramine or the like are illustrations; as noradrenaline reuptake inhibitors, bupropion, GW-320659 or the like are illustrations; as noradrenaline releasing stimulants, rolipram, YM-992 or the like are illustrations; as β_2 -adrenoceptor agonists, amphetamine, dextroamphetamine, phentermine, benzphetamine, methamphetamine, phendimetrazine, phenmetrazine, diethylpropion, phenylpropanolamine, clobenzorex or the like are illustrations; as dopamine agonists, ER-230, doprexin, bromocriptine mesylate or the like are illustrations; as cannabinoid receptor antagonists, rimonabant or the like are illustrations; as γ -aminobutyric acid receptor antagonists, topiramate or the like are illustrations; as H₃-histamine antagonists, GT-2394 or the like are illustrations; as leptin, leptin analogues or leptin receptor agonists, LY-355101 or the like are illustrations; as cholecystokinin agonists (especially CCK-A agonists), SR-146131, SSR-125180, BP-3.200, A-71623, FPL-15849, GI-248573, GW-7178, GI-181771, GW-7854, A-71378 or the like are illustrations; and as neuropeptide Y antagonists, SR-120819-A, PD-160170, NGD-95-1, BIBP-3226, 1229-U-91, CGP-71683, BIBO-3304, CP-671906-01, J-115814 or the like are illustrations. Appetite suppressants are used preferably for diabetes, diabetic complications, obesity, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia or gout, and more preferably for obesity because of stimulating or inhibiting the activities of intracerebral monoamines or bioactive peptides in central appetite regulatory system and suppressing the appetite, leading to reduction of energy intake.

[0066] As angiotensin-converting enzyme inhibitors, captopril, enalapril maleate, alacepril, delapril hydrochloride, ramipril, lisinopril, imidapril hydrochloride, benazepril hydrochloride, ceronapril monohydrate, cilazapril, sodium fosinopril, perindopril erbumine, calcium moveltipril, quinapril hydrochloride, spirapril hydrochloride, temocapril hydrochloride, trandolapril, calcium zofenopril, moexipril hydrochloride, rentiapril or the like are illustrations.

Angiotensin-converting enzyme inhibitors are preferably used for diabetic complications or hypertension.

[0067] As neutral endopeptidase inhibitors, omapatrilat, MDL-100240, fasidotril, sampatrilat, GW-660511X, mixanpril, SA-7060, E-4030, SLV-306, ecadotril or the like are illustrations. Neutral endopeptidase inhibitors are preferably used for diabetic complications or hypertension.

[0068] As angiotensin II receptor antagonists, candesartan cilexetil, candesartan cilexetil/hydrochlorothiazide, potassium losartan, eprosartan mesylate, valsartan, telmisartan, irbesartan, EXP-3174, L-158809, EXP-3312, olmesartan, tasosartan, KT-3-671, GA-0113, RU-64276, EMD-90423, BR-9701 or the like are illustrations. Angiotensin II

receptor antagonists are preferably used for diabetic complications or hypertension.

[0069] As endothelin-converting enzyme inhibitors, CGS-31447, CGS-35066, SM-19712 or the like are illustrations; as endothelin receptor antagonists, L-749805, TBC-3214, BMS-182874, BQ-610, TA-0201, SB-215355, PD-180988, sodium sitaxsentan, BMS-193884, darusentan, TBC-3711, bosentan, sodium tezosentan, J-104132, YM-598, S-0139, SB-234551, RPR-118031A, ATZ-1993, RO-61-1790, ABT-546, enlasentan, BMS-207940 or the like are illustrations. These drugs are preferably used for diabetic complications or hypertension, and more preferably for hypertension.

[0070] As diuretic agents, chlorthalidone, metolazone, cyclopentiazide, trichloromethiazide, hydrochlorothiazide, hydroflumethiazide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, indapamide, triamide, mefruside (azosemide, etacrynic acid, torasemide, piretanide, furosemide, bumetanide, meticrane, potassium canrenoate, spironolactone, triamterene, aminophylline, cicletanine hydrochloride, LLU- α , PNU-80873A, isosorbide, D-mannitol, D-sorbitol, fructose, glycerin, acetazolamide, methazolamide, FR-179544, OPC-31260, lixivaptan, conivaptan hydrochloride or the like are illustrations. Diuretic drugs are preferably used for diabetic complications, hypertension, congestive heart failure or edema, and more preferably for hypertension, congestive heart failure or edema because of reducing blood pressure or improving edema by increasing urinary excretion.

[0071] As calcium antagonists, aranidipine, efonidipine hydrochloride, nicardipine hydrochloride, bamidipine hydrochloride, benidipine hydrochloride, manidipine hydrochloride, cilnidipine, nisoldipine, nitrendipine, nifedipine, nilvadipine, felodipine, amlodipine besilate, pranidipine, lercanidipine hydrochloride, isradipine, elgodipine, azelnidipine, lacidipine, vatanidipine hydrochloride, lemidipine, diltiazem hydrochloride, cletiazem maleate, verapamil hydrochloride, S-verapamil, fasudil hydrochloride, bepridil hydrochloride, gallopamil hydrochloride or the like are illustrations; as vasodilating antihypertensive agents, indapamide, todralazine hydrochloride, hydralazine hydrochloride, cadralazine, budralazine or the like are illustrations; as sympathetic blocking agents, amosulalol hydrochloride, terazosin hydrochloride, bunazosin hydrochloride, prazosin hydrochloride, doxazosin mesylate, propranolol hydrochloride, atenolol, metoprolol tartrate, carvedilol, nipradilol, celiprolol hydrochloride, nebivolol, betaxolol hydrochloride, pindolol, tertatolol hydrochloride, bevantolol hydrochloride, timolol maleate, carteolol hydrochloride, bisoprolol hemifumarate, bopindolol malonate, nipradilol, penbutolol sulfate, acebutolol hydrochloride, tilisolol hydrochloride, nadolol, urapidil, indoramin or the like are illustrations; as centrally acting antihypertensive agents, reserpine or the like are illustrations; and as α_2 -adrenoceptor agonists, clonidine hydrochloride, methyl dopa, CHF-1035, guanabenz acetate, guanfacine hydrochloride, moxonidine, lofexidine, talipexole hydrochloride or the like are illustrations. These drugs are preferably used for hypertension.

[0072] As antiplatelets agents, ticlopidine hydrochloride, dipyridamole, cilostazol, ethyl icosapentate, sarpogrelate hydrochloride, dilazep dihydrochloride, trapidil, beraprost sodium, aspirin or the like are illustrations. Antiplatelets agents are preferably used for atherosclerosis or congestive heart failure.

[0073] As uric acid synthesis inhibitors, allopurinol, oxypurinol or the like are illustrations; as uricosuric agents, benzbromarone, probenecid or the like are illustrations; and as urinary alkalinizers, sodium hydrogen carbonate, potassium citrate, sodium citrate or the like are illustrations. These drugs are preferably used for hyperuricemia or gout.

[0074] In case of use in combination with drugs other than SGLT2 inhibitors, for example, in the use for diabetes, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist and an appetite suppressant is preferable; the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue and an amylin agonist is more preferable; and the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer and an insulin preparation is most preferable. Similarly, in the use for diabetic complications, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin ana-

logue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproduct formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhidantoin, EGB-761, bimoclomol, sulodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a diuretic agent is preferable; and the combination with at least one member of the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist is more preferable. Furthermore, in the use for obesity, the combination with at least one member of the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a β_3 -adrenoceptor agonist and an appetite suppressant is preferable; and the combination with at least one member of the group consisting of a β_3 -adrenoceptor agonist and an appetite suppressant is more preferable.

[0075] When the pharmaceutical compositions of the present invention are employed in the practical treatment, various dosage forms are used depending on their uses. As examples of the dosage forms, powders, granules, fine granules, dry syrups, tablets, capsules, injections, solutions, ointments, suppositories, poultices and the like are illustrations which are orally or parenterally administered.

[0076] These pharmaceutical compositions can be prepared by admixing with or by diluting and dissolving an appropriate pharmaceutical additive such as excipients, disintegrators, binders, lubricants, diluents, buffers, isotonicities, antiseptics, moistening agents, emulsifiers, dispersing agents, stabilizing agents, dissolving aids and the like, and formulating the mixture in accordance with conventional practice. In case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, they can be prepared by formulating each active ingredient together or individually.

[0077] When the pharmaceutical compositions of the present invention are employed in practical treatment, the dosage of a compound represented by the above general formula (I) or a pharmaceutically acceptable salt thereof as the active ingredient is appropriately decided depending on the age, sex, body weight and degree of symptoms and treatment of each patient, which is approximately within the range of from 0.1 to 1,000mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 300mg per day per adult human in the case of parenteral administration, and the daily dose can be divided into one to several doses per day and administered suitably. Also, in case of the use of the compound of the present invention in combination with the drugs other than SGLT2 inhibitors, the dosage of the compound of the present invention can be decreased appropriately and occasionally depending on the dosage of the drugs other than SGLT2 inhibitors.

[0078] The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. However, the present invention is not limited thereto.

Reference Example 1

1,2-Dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3H-pyrazol-3-one

[0079] To a solution of 4-isopropoxybenzylalcohol (0.34g) in tetrahydrofuran (6mL) were added triethylamine (0.28mL) and methanesulfonyl chloride (0.16mL), and the mixture was stirred at room temperature for 30 minutes. The resulting insoluble material was removed by filtration. The obtained solution of 4-isopropoxybenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 81mg) and methyl acetoacetate (0.20mL) in 1,2-dimethoxyethane (10mL), and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (5mL). Anhydrous hydrazine (0.19mL) was added to the solution, and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3H-pyrazol-3-one (95mg).

¹H-NMR (DMSO-*d*₆) δ ppm:

1.22 (6H, d, J=6.0Hz), 1.99 (3H, s), 3.45 (2H, s), 4.40-4.60 (1H, m), 6.65-6.80 (2H, m), 6.95-7.10 (2H, m)

Reference Example 2

1,2-Dihydro-5-methyl-4-[(4-propylphenyl)methyl]-3H-pyrazol-3-one

- 5 [0080] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-propylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

¹H-NMR (DMSO-d₆) δ ppm:

0.75-0.95 (3H, m), 1.45-1.65 (2H, m), 1.99 (3H, s), 2.40-2.55 (2H, m), 3.32 (2H, s), 6.95-7.10 (4H, m)

10 Reference Example 3

1,2-Dihydro-4-[(4-isobutylphenyl)methyl]-5-methyl-3H-pyrazol-3-one

- 15 [0081] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-isobutylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

¹H-NMR (DMSO-d₆) δ ppm:

0.83 (6H, d, J=6.6Hz), 1.70-1.85 (1H, m), 1.99 (3H, s), 2.30-2.45 (2H, m), 3.50 (2H, s), 6.90-7.10 (4H, m)

20 Reference Example 4

1,2-Dihydro-5-methyl-4-[(4-propoxyphenyl)methyl]-3H-pyrazol-3-one

- 25 [0082] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-propoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

¹H-NMR (DMSO-d₆) δ ppm:

0.95 (3H, t, J=7.4Hz), 1.60-1.75 (2H, m), 1.98 (3H, s), 3.46 (2H, s), 3.75-3.90 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

30 Reference Example 5

4-[(4-Ethoxyphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

- [0083] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-ethoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

35 ¹H-NMR (DMSO-d₆) δ ppm:

1.20-1.35 (3H, m), 1.98 (3H, s), 3.46 (2H, s), 3.85-4.05 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

Reference Example 6

- 40 1,2-Dihydro-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-3H-pyrazol-3-one

[0084] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-trifluoro-methylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol. ¹H-NMR (DMSO-d₆) δ ppm:

2.02 (3H, s), 3.64 (2H, s), 7.30-7.45 (2H, m), 7.55-7.70 (2H, m)

45

Reference Example 7

4-[(4-*tert*-Butylphenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

- 50 [0085] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-*tert*-butylbenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

¹H-NMR (DMSO-d₆) δ ppm:

1.24 (9H, s), 2.01 (3H, s), 3.49 (2H, s), 7.00-7.15 (2H, m), 7.15-7.30 (2H, m)

55

Reference Example 8

4-[(4-Butoxyphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

- 5 [0086] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-butoxybenzyl alcohol instead of 4-isopropoxybenzyl alcohol.

¹H-NMR (DMSO-*d*₆) δ ppm:

0.91 (3H, t, J=7.4Hz), 1.30-1.50 (2H, m), 1.55-1.75 (2H, m), 1.98 (3H, s), 3.46 (2H, s), 3.80-3.95 (2H, m), 6.70-6.85 (2H, m), 6.95-7.10 (2H, m)

10

Reference Example 9

1,2-Dihydro-5-methyl-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one

- 15 [0087] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-(methylthio) benzyl alcohol instead of 4-isopropoxybenzyl alcohol.

¹H-NMR (DMSO-*d*₆) δ ppm:

1.99 (3H, s), 2.42 (3H, s), 3.50 (2H, s), 7.05-7.20 (4H, m)

20 Reference Example 10

5-Ethyl-1,2-dihydro-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one

- 25 [0088] The title compound was prepared in a similar manner to that described in Reference Example 1 using 4-(methylthio) benzyl alcohol instead of 4-isopropoxybenzyl alcohol and using methyl 3-oxopentanoate instead of methyl acetoacetate.

¹H-NMR (DMSO-*d*₆) δ ppm:

1.02 (3H, t, J=7.6Hz), 2.39 (2H, q, J=7.6Hz), 2.42 (3H, s), 3.51 (2H, s), 7.05-7.20 (4H, m)

30 Reference Example 11

1,2-Dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

- 35 [0089] To a suspension of sodium hydride (60%, 40mg) in 1,2-dimethoxyethane (1mL) were added methyl acetoacetate (0.11mL), 4-isopropylbenzyl chloride (0.17g) and a catalytic amount of sodium iodide, and the mixture was stirred at 80°C overnight. The reaction mixture was poured into a saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with diethyl ether. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (1mL). Anhydrous hydrazine (0.094mL) was added to the solution, and the mixture was stirred at 80°C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1,2-dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one (0.12g).

¹H-NMR (DMSO-*d*₆) δ ppm:

1.16 (6H, d, J=6.9Hz), 2.01 (3H, s), 2.70-2.90 (1H, m), 3.49 (2H, s), 6.95-7.20 (4H, m)

45 Reference Example 12

4-[(4-Ethylphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

- 50 [0090] The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-ethylbenzyl chloride instead of 4-isopropylbenzyl chloride.

¹H-NMR (DMSO-*d*₆) δ ppm:

1.13 (3H, t, J=7.6Hz), 2.00 (3H, s), 2.45-2.60 (2H, m), 3.49 (2H, s), 7.00-7.15 (4H, m)

Reference Example 13

55

1,2-Dihydro-5-methyl-4-[(4-methylphenyl)methyl]-3*H*-pyrazol-3-one

- [0091] The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-meth-

ylbenzyl bromide instead of 4-isopropylbenzyl chloride.

¹H-NMR (DMSO-d₆) δ ppm:

1.98 (3H, s), 2.23 (3H, s), 3.48 (2H, s), 6.95-7.10 (4H, m)

5 Reference Example 14

4-Benzyl-1,2-dihydro-5-trifluoromethyl-3*H*-pyrazol-3-one

[0092] The title compound was prepared in a similar manner to that described in Reference Example 11 using ethyl trifluoro-acetoacetate instead of methyl acetoacetate and using benzyl bromide instead of 4-isopropylbenzyl chloride.

¹H-NMR (DMSO-d₆) δ ppm:

3.73 (2H, s), 7.05-7.35 (5H, m), 12.50-13.10 (1H, brs)

Reference Example 15

15 1,2-Dihydro-4-[(4-methoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

[0093] The title compound was prepared in a similar manner to that described in Reference Example 11 using 4-methoxybenzyl bromide instead of 4-isopropylbenzyl chloride.

20 ¹H-NMR (DMSO-d₆) δ ppm:

1.99 (3H, s), 3.47 (2H, s), 3.69 (3H, s), 6.75-6.85 (2H, m), 7.00-7.10 (2H, m), 8.70-11.70 (2H, br)

Reference Example 16

25 4-Benzyl-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one

[0094] The title compound was prepared in a similar manner to that described in Reference Example 11 using benzyl bromide instead of 4-isopropylbenzyl chloride.

¹H-NMR (DMSO-d₆) δ ppm:

30 2.00 (3H, s), 3.54 (2H, s), 7.05-7.30 (5H, s)

Reference Example 17

35 4-[(4-Isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0095] To a suspension of 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3*H*-pyrazol-3-one (46mg), aceto-bromo-α-D-glucose (99mg) and 4A molecular sieves in tetrahydrofuran (3mL) was added silver carbonate (66mg), and the mixture was stirred under shading the light at 65°C overnight. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran). Further purification by preparative thin layer chromatography on silica gel (developing solvent: ethyl acetate/hexane = 2/1) afforded 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (42mg).

¹H-NMR (CDCl₃) δ ppm:

45 1.25-1.35 (6H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 4.40-4.55 (1H, m), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.05 (2H, m).

Reference Example 18

50 5-Methyl-4-[(4-propylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole

[0096] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-propylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

55 0.91 (3H, t, J=7.3Hz), 1.50-1.65 (2H, m), 1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 2.45-2.55 (2H, m), 3.55 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.30 (1H, dd, J=3.9, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 7.00-7.20 (4H, m)

Reference Example 19

4-[(4-Isobutylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

- 5 [0097] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-4-[(4-isobutylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

- 0.87 (6H, d, J=6.6Hz), 1.70-1.85 (1H, m), 1.87 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 2.40 (2H, d, J=7.2Hz), 3.56 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.95-7.10 (4H, m)

Reference Example 20

- 15 5-Methyl-4-[(4-propoxyphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

[0098] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-propoxyphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one

- 20 ¹H-NMR (CDCl₃) δ ppm:

1.01 (3H, t, J=7.4Hz), 1.70-1.85 (2H, m), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.53 (1H, d, J=15.7Hz), 3.59 (1H, d, J=15.7Hz), 3.80-3.95 (3H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m).

- 25 Reference Example 21

4-[(4-Ethoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

- 30 [0099] The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-ethoxy-phenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

- 1.38 (3H, t, J=7.0Hz), 1.89 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.53 (1H, d, J=15.8Hz), 3.59 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 3.98 (2H, q, J=7.0Hz), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

Reference Example 22

- 40 5-Methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-4-[(4-trifluoromethylphenyl)methyl]-1*H*-pyrazole

[0100] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

- 45 1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.14 (3H, s), 3.65 (1H, d, J=15.9Hz), 3.71 (1H, d, J=15.9Hz), 3.80-3.90 (1H, m), 4.14 (1H, dd, J=2.4, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.40 (3H, m), 5.55-5.65 (1H, m), 7.20-7.30 (2H, m), 7.45-7.55 (2H, m)

Reference Example 23

- 50 4-[(4-*tert*-Butylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

- [0101] The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-*tert*-butyl-phenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

- 1.27 (9H, s), 1.84 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.14 (3H, s), 3.56 (1H, d, J=15.8Hz), 3.64 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60

(1H, m), 7.00-7.10 (2H, m), 7.20-7.30 (2H, m)

Reference Example 24

5 4-[(4-Butoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

[0102] The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-butoxy-phenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

10 ¹H-NMR (CDCl₃) δ ppm:

0.96 (3H, t, J=7.4Hz), 1.40-1.55 (2H, m), 1.65-1.80 (2H, m), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 3.52 (1H, d, J=15.8Hz), 3.59 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 3.91 (2H, t, J=6.5Hz), 4.13 (1H, dd, J=2.3, 12.4Hz), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 6.95-7.10 (2H, m)

15 Reference Example 25

5-Methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

[0103] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

20 ¹H-NMR (CDCl₃) δ ppm:

1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.12 (3H, s), 2.44 (3H, s), 3.50-3.65 (2H, m), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.4, 12.4Hz), 4.31 (1H, dd, J=4.1, 12.4Hz), 5.15-5.30 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m), 8.65-8.85 (1H, brs)

Reference Example 26

30 5-Ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

[0104] The title compound was prepared in a similar manner to that described in Reference Example 17 using 5-ethyl-1,2-dihydro-4-[(4-methylthiophenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

35 ¹H-NMR (CDCl₃) δ ppm:

1.13 (3H, t, J=7.6Hz), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 2.45-2.55 (2H, m), 3.50-3.70 (2H, m), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m), 8.80-9.20 (1H, brs)

Reference Example 27

40 4-[(4-Isopropylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

[0105] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-4-[(4-isopropylphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

45 ¹H-NMR (CDCl₃) δ ppm:

1.20 (6H, d, J=6.9Hz), 1.85 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.13 (3H, s), 2.75-2.90 (1H, m), 3.56 (1H, d, J=15.8Hz), 3.63 (1H, d, J=15.8Hz), 3.80-3.90 (1H, m), 4.05-4.20 (1H, m), 4.31 (1H, dd, J=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 7.00-7.15 (4H, m), 8.70-9.30 (1H, brs)

50

Reference Example 28

4-[(4-Methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

55 [0106] To a solution of 1,2-dihydro-4-[(4-methylthiophenyl)-methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one (2.0g) in acetonitrile (100mL) were added acetobromo- α -D-glucose (3.1g) and potassium carbonate (1.1g), and the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and

brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/1) to give 4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole (2.0g).

¹H-NMR (CDCl₃) δ ppm:

- 5 1.91 (3H, s), 2.03 (3H, s), 2.04 (3H, s), 2.09 (3H, s), 2.45 (3H, s), 3.73 (2H, s), 3.75-3.90 (1H, m), 4.15-4.35 (2H, m), 5.15-5.65 (4H, m), 7.00-7.20 (4H, m)

Reference Example 29

10 4-Benzyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0107] The title compound was prepared in a similar manner to that described in Reference Example 28 using 4-benzyl-1,2-dihydro-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one.

15 ¹H-NMR (CDCl₃) δ ppm:

- 1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.08 (3H, s), 3.70-3.90 (3H, m), 4.15-4.30 (2H, m), 5.10-5.50 (4H, m), 7.10-7.30 (5H, m)

Reference Example 30

20

4-[(4-Methoxyphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

[0108] The title compound was prepared in a similar manner to that described in Reference Example 28 using 1,2-dihydro-4-[(4-methoxyphenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3*H*-pyrazol-3-one.

25 ¹H-NMR (CDCl₃) δ ppm:

- 1.93 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.09 (3H, s), 3.65-3.75 (2H, m), 3.77 (3H, s), 3.75-3.90 (1H, m), 4.15-4.35 (2H, m), 5.10-5.45 (4H, m), 6.75-6.85 (2H, m), 7.00-7.15 (2H, m)

30 Reference Example 31

4-[(4-Methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

[0109] The title compound was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-4-[(4-methoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

- 35 1.89 (3H, s), 2.02 (3H, s), 2.03 (3H, s), 2.05 (3H, s), 2.10 (3H, s), 3.45-3.65 (2H, m), 3.76 (3H, s), 3.80-3.90 (1H, m), 4.11 (1H, dd, *J*=2.2, 12.4Hz), 4.30 (1H, dd, *J*=4.0, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.60 (1H, m), 6.70-6.85 (2H, m), 7.00-7.10 (2H, m)

Reference Example 32

4-Benzyl-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole

45

[0110] The title compound was prepared in a similar manner to that described in Reference Example 17 using 4-benzyl-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)methyl]-5-methyl-3*H*-pyrazol-3-one.

¹H-NMR (CDCl₃) δ ppm:

- 50 1.86 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 3.59 (1H, d, *J*=15.8Hz), 3.66 (1H, d, *J*=15.8Hz), 3.80-3.90 (1H, m), 4.11 (1H, dd, *J*=2.3, 12.4Hz), 4.30 (1H, dd, *J*=4.0, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.65 (1H, m), 7.05-7.30 (5H, m), 8.75-9.55 (1H, brs)

Reference Example 33

55 4-[(4-Methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)pyrazole

[0111] A suspension of 4-[(4-methoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole (18mg), potassium carbonate (14mg) and iodomethane (4.7mg) in acetonitrile (2mL) was stirred at 75°C

overnight. The reaction mixture was filtered through celite®, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (developing solvent: benzene/acetone = 2/1) to give 4-[(4-methoxyphenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)pyrazole (4mg).

5 ¹H-NMR (CDCl₃) δ ppm:

1.90 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.07 (3H, s), 3.45-3.60 (2H, m), 3.60 (3H, s), 3.76 (3H, s), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.4, 12.4Hz), 4.29 (1H, dd, J=4.1, 12.4Hz), 5.15-5.30 (3H, m), 5.50-5.60 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

10 Reference Example 34

1-Methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole

15 **[0112]** A suspension of 4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole (30mg), potassium carbonate (8.0mg) and iodomethane (8.2mg) in tetrahydrofuran (1mL) was stirred at 75°C overnight. The reaction mixture was filtered through celite®, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (developing solvent: dichloromethane/ethyl acetate = 5/1) to give 1-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole (13mg).

20 ¹H-NMR (CDCl₃) δ ppm:

1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.44 (3H, s), 3.65-3.95 (6H, m), 4.14 (1H, dd, J=2.3, 12.4Hz), 4.29 (1H, dd, J=4.3, 12.4Hz), 5.15-5.35 (3H, m), 5.50-5.65 (1H, m), 7.00-7.20 (4H, m)

Reference Example 35

25

1-Ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole

[0113] The title compound was prepared in a similar manner to that described in Reference Example 34 using iodoethane instead of iodomethane.

30 ¹H-NMR (CDCl₃) δ ppm:

1.40 (3H, t, J=7.2Hz), 1.90 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 3.72 (2H, s), 3.80-3.90 (1H, m), 4.05-4.20 (3H, m), 4.27 (1H, dd, J=4.5, 12.4Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m)

35 Reference Example 36

4-[(4-Methylthiophenyl)methyl]-1-propyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-5-trifluoromethylpyrazole

40 **[0114]** The title compound was prepared in a similar manner to that described in Reference Example 34 using 1-iodopropane instead of iodomethane.

¹H-NMR (CDCl₃) δ ppm:

0.92 (3H, t, J=7.4Hz), 1.75-1.90 (2H, m), 1.89 (3H, s), 2.02 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.44 (3H, s), 3.72 (2H, s), 3.80-3.90 (1H, m), 3.90-4.05 (2H, m), 4.12 (1H, dd, J=2.3, 12.4Hz), 4.27 (1H, dd, J=4.5, 12.4Hz), 5.10-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.10-7.20 (2H, m)

45

Reference Example 37

3-(β-D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

50 **[0115]** To a solution of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1*H*-pyrazole (61mg) in ethanol (3mL) was added 1 mol/L aqueous sodium hydroxide solution (0.53mL), and the mixture was stirred at room temperature for 2 hours. The solvent was removed under reduced pressure, and the residue was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol) to give 3-(β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole (39mg).

55 ¹H-NMR (CD₃OD) δ ppm:

1.26 (6H, d, J=5.9Hz), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 4.45-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

Reference Example 38

3-(β -D-Glucopyranosyloxy)-5-methyl-4-[(4-propylphenyl)-methyl]-1H-pyrazole

- 5 [0116] The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-propylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

- 0.91 (3H, t, J=7.5Hz), 1.50-1.65 (2H, m), 2.05 (3H, s), 2.45-2.60 (2H, m), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.83
10 (1H, d, J=11.9Hz), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Example 39

3-(β -D-Glucopyranosyloxy)-4-[(4-isobutylphenyl)methyl]-5-methyl-1H-pyrazole

- 15 [0117] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-isobutylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

- 20 0.87 (6H, d, J=6.6Hz), 1.70-1.90 (1H, m), 2.04 (3H, s), 2.41 (2H, d, J=7.1Hz), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m),
5.00-5.10 (1H, m), 6.95-7.15 (4H, m)

Reference Example 40

- 25 3-(β -D-Glucopyranosyloxy)-5-methyl-4-[(4-propoxyphenyl)-methyl]-1H-pyrazole

[0118] The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-propoxyphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

30 ¹H-NMR (CD₃OD) δ ppm:

- 1.02 (3H, t, J=7.4Hz), 1.65-1.80 (2H, m), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (3H, m),
5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

Reference Example 41

- 35 4-[(4-Ethoxyphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1H-pyrazole

- [0119] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-ethoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

40 ¹H-NMR (CD₃OD) δ ppm:

- 1.34 (3H, t, J=7.0Hz), 2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (1H, m), 3.97 (2H, q, J=7.0Hz),
5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

- 45 Reference Example 42

3-(β -D-Glucopyranosyloxy)-5-methyl-4-[(4-trifluoromethylphenyl)methyl]-1H-pyrazole

- 50 [0120] The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-4-[(4-trifluoromethylphenyl)methyl]-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

- 2.08 (3H, s), 3.20-3.40 (4H, m), 3.67 (1H, dd, J=5.0, 11.9Hz), 3.75-3.90 (3H, m), 5.00-5.10 (1H, m), 7.30-7.45 (2H, m),
7.45-7.60 (2H, m)

55

Reference Example 43

4-[(4-*tert*-Butylphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

- 5 [0121] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-*tert*-butyl-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

1.28 (9H, s), 2.06 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 7.05-7.15 (2H, m), 7.20-7.30 (2H, m)

10

Reference Example 44

4-[(4-Butoxyphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

- 15 [0122] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-butoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

0.97 (3H, t, J=7.4Hz), 1.40-1.55 (2H, m), 1.65-1.80 (2H, m), 2.05 (3H, s), 3.30-3.45 (4H, m), 3.60-3.75 (3H, m), 3.83 (1H, d, J=12.0Hz), 3.91 (2H, t, J=6.4Hz), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

20

Reference Example 45

3-(β -D-Glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)-methyl]-1*H*-pyrazole

25

- [0123] The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

2.06 (3H, s), 2.42 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.05-7.20 (4H, m)

30

Reference Example 46

5-Ethyl-3-(β -D-glucopyranosyloxy)-4-[(4-methylthiophenyl)-methyl]-1*H*-pyrazole

35

- [0124] The title compound was prepared in a similar manner to that described in Reference Example 37 using 5-ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

1.06 (3H, t, J=7.6Hz), 2.42 (3H, s), 2.47 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.10-7.20 (4H, m)

40

Reference Example 47

3-(β -D-Glucopyranosyloxy)-4-[(4-isopropylphenyl)methyl]-5-methyl-1*H*-pyrazole

45

- [0125] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-isopropyl-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

1.20 (6H, d, J=6.9Hz), 2.05 (3H, s), 2.75-2.90 (1H, m), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

50

Reference Example 48

3-(β -D-Glucopyranosyloxy)-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-1*H*-pyrazole

55

- [0126] The title compound was prepared in a similar manner to that described in Reference Example 37 using

4-[(4-methyl-thiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.
¹H-NMR (CD₃OD) δ ppm: 2.42 (3H, s), 3.25-3.50 (4H, m), 3.69 (1H, dd, *J*=4.9, 12.0 Hz), 3.75-3.90 (3H, m), 4.90-5.10 (1H, m), 7.10-7.20 (4H, m)

5

Reference Example 49

4-Benzyl-3-(β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole

10 [0127] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-benzyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoro-methyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

3.25-3.45 (4H, m), 3.67 (1H, dd, *J*=5.3, 12.0 Hz), 3.80-3.95 (3H, m), 4.97 (1H, d, *J*=7.4 Hz), 7.05-7.25 (5H, m)

15

Reference Example 50

3-(β -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-trifluoromethyl-1*H*-pyrazole

20 [0128] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methoxy-phenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

3.25-3.45 (4H, m), 3.67 (1H, d, *J*=5.4, 12.1 Hz), 3.73 (3H, s), 3.75-3.90 (3H, m), 4.90-5.00 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

25

Reference Example 51

3-(β -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

30

[0129] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

2.04 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.73 (3H, s), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 6.75-6.85 (2H, m), 7.05-7.15 (2H, m)

35

Reference Example 52

4-Benzyl-3-(β -D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

40

[0130] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-benzyl-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

2.05 (3H, s), 3.25-3.45 (4H, m), 3.60-3.90 (4H, m), 5.00-5.10 (1H, m), 7.05-7.25 (5H, m)

45

Reference Example 53

3-(β -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-1,5-dimethylpyrazole

50

[0131] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methoxy-phenyl)methyl]-1,5-dimethyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)pyrazole instead of 4-[(4-isopropoxy-phenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

2.06 (3H, s), 3.25-3.45 (4H, m), 3.55-3.70 (6H, m), 3.73 (3H, s), 3.75-3.90 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.05-7.15 (2H, m)

55

Reference Example 54

3-(β -D-Glucopyranosyloxy)-1-methyl-4-[(4-methylthiophenyl)-methyl]-5-trifluoromethylpyrazole

- 5 [0132] The title compound was prepared in a similar manner to that described in Reference Example 37 using 1-methyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

2.42 (3H, s), 3.30-3.50 (4H, m), 3.69 (1H, dd, *J*=4.7, 12.0Hz), 3.75-3.90 (6H, m), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

10

Reference Example 55

1-Ethyl-3-(β -D-glucopyranosyloxy)-4-[(4-methylthiophenyl)-methyl]-5-trifluoromethylpyrazole

- 15 [0133] The title compound was prepared in a similar manner to that described in Reference Example 37 using 1-ethyl-4-[(4-methylthiophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

1.38 (3H, t, *J*=7.1Hz), 2.42 (3H, s), 3.30-3.50 (4H, m), 3.60-3.75 (1H, m), 3.75-3.90 (3H, m), 4.14 (2H, q, *J*=7.1Hz),

20

5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Reference Example 56

3-(β -D-Glucopyranosyloxy)-4-[(4-methylthiophenyl)methyl]-1-propyl-5-trifluoromethylpyrazole

25

- [0134] The title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methylthio-phenyl)methyl]-1-propyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethylpyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

30

0.90 (3H, t, *J*=7.4Hz), 1.75-1.90 (2H, m), 2.42 (3H, s), 3.30-3.50 (4H, m), 3.69 (1H, dd, *J*=4.9, 12.0Hz), 3.75-3.90 (3H, m), 4.00-4.10 (2H, m), 5.25-5.35 (1H, m), 7.05-7.20 (4H, m)

Reference Example 57

35

3-(β -D-Glucopyranosyloxy)-5-methyl-4-[(4-methylphenyl)-methyl]-1*H*-pyrazole

- [0135] 5-Methyl-4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole was prepared in a similar manner to that described in Reference Example 17 using 1,2-dihydro-5-methyl-4-[(4-methylphenyl)methyl]-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3*H*-pyrazol-3-one.

40

Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 5-methyl-4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole. ¹H-NMR (CD₃OD) δ ppm:

2.04 (3H, s), 2.26 (3H, s), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.15 (4H, m)

45

Reference Example 58

4-[(4-Ethylphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole

50

- [0136] 4-[(4-Ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole was prepared in a similar manner to that described in Reference Example 17 using 4-[(4-ethylphenyl)methyl]-1,2-dihydro-5-methyl-3*H*-pyrazol-3-one instead of 1,2-dihydro-4-[(4-isopropoxyphenyl)-methyl]-5-methyl-3*H*-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-ethylphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1*H*-pyrazole. ¹H-NMR (CD₃OD) δ ppm:

55

1.18 (3H, t, *J*=7.6Hz), 2.04 (3H, s), 2.57 (2H, q, *J*=7.6Hz), 3.25-3.45 (4H, m), 3.55-3.90 (4H, m), 5.00-5.10 (1H, m), 6.95-7.20 (4H, m)

Reference Example 59

3-(β -D-Glucopyranosyloxy)-4-[(4-methylphenyl)methyl]-5-trifluoromethyl-1H-pyrazole

- 5 **[0137]** 4-[(4-Methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference Example 28 using 1,2-dihydro-4-[(4-methylphenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-methylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

2.25 (3H, s), 3.20-3.45 (4H, m), 3.55-3.70 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 6.90-7.15 (4H, m)

15 Reference Example 60

4-[(4-Ethylphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

- 20 **[0138]** 4-[(4-Ethylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference Example 28 using 4-[(4-ethylphenyl)methyl]-1,2-dihydro-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-ethylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

25 ¹H-NMR (CD₃OD) δ ppm:

1.18 (3H, t, J=7.6Hz), 2.50-2.60 (2H, m), 3.15-3.40 (4H, m), 3.55-3.65 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 6.95-7.15 (4H, m)

Reference Example 61

30

3-(β -D-Glucopyranosyloxy)-4-[(4-isopropylphenyl)methyl]-5-trifluoromethyl-1H-pyrazole

- [0139]** 4-[(4-Isopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference Example 28 using 1,2-dihydro-4-[(4-isopropylphenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-isopropylphenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole. ¹H-NMR (CD₃OD) δ ppm:

40 1.20 (6H, d, J=6.9Hz), 2.75-2.85 (1H, m), 3.15-3.40 (4H, m), 3.55-3.65 (1H, m), 3.70-3.90 (3H, m), 4.80-4.95 (1H, m), 7.00-7.15 (4H, m)

Reference Example 62

45

4-[(4-Chlorophenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole

- [0140]** 4-[(4-Chlorophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole was prepared in a similar manner to that described in Reference Example 28 using 4-[(4-chlorophenyl)methyl]-1,2-dihydro-5-trifluoromethyl-3H-pyrazol-3-one instead of 1,2-dihydro-4-[(4-methylthiophenyl)methyl]-5-trifluoromethyl-3H-pyrazol-3-one. Then, the title compound was prepared in a similar manner to that described in Reference Example 37 using 4-[(4-chlorophenyl)methyl]-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-5-trifluoromethyl-1H-pyrazole instead of 4-[(4-isopropoxyphenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-*O*-acetyl- β -D-glucopyranosyloxy)-1H-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

50 3.20-3.40 (4H, m), 3.55-3.70 (1H, m), 3.75-3.90 (3H, m), 4.80-4.95 (1H, m), 7.10-7.25 (4H, m)

55

Reference Example 63

3-(β -D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1-propylpyrazole

- 5 **[0141]** To a suspension of 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole (50mg) and cesium carbonate (0.20g) in *N,N*-dimethylformamide (1mL) was added 1-iodopropane (0.036mL) at 50°C, and the mixture was stirred overnight. Water was added to the reaction mixture, and the resulting mixture was purified by solid phase extraction on ODS (washing solvent: distilled water, eluent: methanol). The resulting semi-purified material was purified by column chromatography on silica gel (eluent: dichloromethane/ methanol = 8/1) to give 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1-propylpyrazole (28mg).
- 10 ¹H-NMR (CD₃OD) δ ppm:
 0.87 (3H, t, J=7.4Hz), 1.26 (6H, d, J=6.0Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.95 (3H, m), 4.40-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

15 Reference Example 64

1-Ethyl-3-(β -D-glucopyranosyloxy)-4-[(4-isopropylphenyl)-methyl]-5-methylpyrazole

- 20 **[0142]** The title compound was prepared in a similar manner to that described in Reference Example 63 using iodoethane instead of 1-iodopropane.
- ¹H-NMR (CD₃OD) δ ppm:
 1.26 (6H, d, J=6.0Hz), 1.29 (3H, t, J=7.2Hz), 2.08 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.90 (1H, m), 3.96 (2H, q, J=7.2Hz), 4.40-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

25 Reference Example 65

1-Ethyl-3-(β -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)-methyl]-5-methylpyrazole

- 30 **[0143]** The title compound was prepared in a similar manner to that described in Reference Example 63 using 3-(β -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1H-pyrazole instead of 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole and using iodoethane instead of 1-iodopropane.
- ¹H-NMR (CD₃OD) δ ppm:
 1.29 (3H, t, J=7.1Hz), 2.07 (3H, s), 3.20-3.45 (4H, m), 3.55-3.75 (6H, m), 3.82 (1H, dd, J=2.0, 12.0Hz), 3.90-4.05 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.05-7.15 (2H, m)

35 Reference Example 66

3-(β -D-Glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1-propylpyrazole

- 40 **[0144]** The title compound was prepared in a similar manner to that described in Reference Example 63 using 3-(β -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methyl-1H-pyrazole instead of 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole.
- ¹H-NMR (CD₃OD) δ ppm:
 0.87 (3H, t, J=7.5Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.35-3.45 (4H, m), 3.60-3.75 (3H, m), 3.73 (3H, s), 3.75-3.85 (1H, m), 3.85-3.95 (2H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)
- 45

Reference Example 67

1-Ethyl-4-[(4-ethoxyphenyl)methyl]-3-(β -D-glucopyranosyl-oxy)-5-methylpyrazole

- 50 **[0145]** The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethoxyphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1H-pyrazole and using iodoethane instead of 1-iodopropane.
- ¹H-NMR (CD₃OD) δ ppm:
 1.28 (3H, t, J=7.4Hz), 1.34 (3H, t, J=7.2Hz), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.85 (1H, m), 3.90-4.00 (4H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)
- 55

Reference Example 68

4-[(4-Ethoxyphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1-propylpyrazole

- 5 [0146] The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethoxy-phenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-(β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methyl-1H-pyrazole.

¹H-NMR (CD₃OD) δ ppm:

- 10 0.87 (3H, t, J=7.6Hz), 1.34 (3H, t, J=7.1Hz), 1.65-1.80 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.81 (1H, dd, J=2.1, 12.1Hz), 3.85-4.05 (4H, m), 5.00-5.10 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m)

Reference Example 69

1-Ethyl-4-[(4-ethylphenyl)methyl]-3-(β -D-glucopyranosyl-oxy)-5-methylpyrazole

- 15 [0147] The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethyl-phenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-(β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methyl-1H-pyrazole and using iodoethane instead of 1-iodopropane.

¹H-NMR (CD₃OD) δ ppm:

- 20 1.17 (3H, t, J=7.6Hz), 1.28 (3H, t, J=7.2Hz), 2.06 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.75-3.85 (1H, m), 3.90-4.00 (2H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Reference Example 70

- 25 4-[(4-Ethylphenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1-propylpyrazole

[0148] The title compound was prepared in a similar manner to that described in Reference Example 63 using 4-[(4-ethyl-phenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1H-pyrazole instead of 3-(β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methyl-1H-pyrazole.

- 30 ¹H-NMR (CD₃OD) δ ppm:

0.87 (3H, t, J=7.4Hz), 1.17 (3H, t, J=7.6Hz), 1.65-1.80 (2H, m), 2.06 (3H, s), 2.56 (2H, q, J=7.6Hz), 3.25-3.45 (4H, m), 3.60-3.95 (6H, m), 5.00-5.10 (1H, m), 7.00-7.15 (4H, m)

Reference Example 71

- 35 1-Butyl-3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-5-methylpyrazole

[0149] The title compound was prepared in a similar manner to that described in Reference Example 63 using 1-bromobutane instead of 1-iodopropane.

- 40 ¹H-NMR (CD₃OD) δ ppm:

0.92 (3H, t, J=7.4Hz), 1.20-1.40 (8H, m), 1.60-1.75 (2H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.55-3.75 (3H, m), 3.81 (1H, dd, J=2.1, 12.0Hz), 3.91 (2H, t, J=7.2Hz), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

- 45 Reference Example 72

3-(β -D-Glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

- 50 [0150] The title compound was prepared in a similar manner to that described in Reference Example 63 using 2-bromopropane instead of 1-iodopropane.

¹H-NMR (CD₃OD) δ ppm:

1.26 (6H, d, J=6.0Hz), 1.30-1.40 (6H, m), 2.08 (3H, s), 3.15-3.45 (4H, m), 3.55-3.75 (3H, m), 3.78 (1H, dd, J=2.3, 12.0Hz), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

55

Reference Example 73

4-[(4-Ethylthiophenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one

- 5 **[0151]** To a solution of 4-ethylthiobenzyl alcohol (8.3g) and triethylamine (6.9mL) in tetrahydrofuran (200mL) was added methanesulfonyl chloride (3.8mL) at 0°C, and the mixture was stirred for 1 hour. Insoluble material was removed by filtration. The obtained solution of 4-ethylthiobenzyl methanesulfonate in tetrahydrofuran was added to a suspension of sodium hydride (60%, 2.2g) and methyl acetoacetate (5.3mL) in 1,2-dimethoxyethane (200mL), and the mixture was stirred at 80°C overnight. A saturated aqueous sodium hydrogen carbonate solution was added to the reaction mixture, and the resulting mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. To a solution of the residue in toluene (150mL) was added hydrazine monohydrate (7.2mL), and the mixture was stirred at 80°C for 1 hour. The reaction mixture was cooled to 0°C and stirred for additional 1 hour. The resulting precipitates were collected by filtration and washed with water and hexane to give 4-[(4-ethylthiophenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one (1.5g).
- 15 ¹H-NMR (DMSO-d₆) δ ppm:
1.19 (3H, t, J=7.3Hz), 2.00 (3H, s), 2.90 (2H, q, J=7.3Hz), 3.51 (2H, s), 7.05-7.15 (2H, m), 7.15-7.25 (2H, m)

Reference Example 74

4-[(4-Ethylthiophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole

- [0152]** To a suspension of 4-[(4-ethylthiophenyl)methyl]-1,2-dihydro-5-methyl-3H-pyrazol-3-one (1.6g) and aceto-bromo-α-D-glucose (2.9g) in tetrahydrofuran (30mL) was added silver carbonate (2.1g), and the mixture was stirred under shading the light at 60°C overnight. The reaction mixture was purified by column chromatography on aminopropyl silica gel (eluent: tetrahydrofuran) and further column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/3) to give 4-[(4-ethylthiophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole (1.4g).
- 25 ¹H-NMR (CDCl₃) δ ppm:
1.28 (3H, t, J=7.4Hz), 1.88 (3H, s), 2.01 (3H, s), 2.03 (3H, s), 2.06 (3H, s), 2.11 (3H, s), 2.89 (2H, q, J=7.4Hz), 3.56 (1H, d, J=15.9Hz), 3.62 (1H, d, J=15.9Hz), 3.80-3.90 (1H, m), 4.13 (1H, dd, J=2.3, 12.6Hz), 4.31 (1H, dd, J=3.9, 12.6Hz), 5.15-5.35 (3H, m), 5.55-5.65 (1H, m), 7.00-7.10 (2H, m), 7.15-7.25 (2H, m), 8.79 (1H, brs)
- 30

Reference Example 75

4-[(4-Ethylthiophenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1H-pyrazole

- 35 **[0153]** To a solution of 4-[(4-ethylthiophenyl)methyl]-5-methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)-1H-pyrazole (1.3g) in methanol (10mL) was added sodium methoxide (28% methanol solution, 0.13mL), and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloro-methane/methanol = 5/1) to give 4-[(4-ethylthiophenyl)methyl]-3-(β-D-glucopyranosyloxy)-5-methyl-1H-pyrazole (0.87g).
- 40 ¹H-NMR (CD₃OD) δ ppm:
1.24 (3H, t, J=7.3Hz), 2.06 (3H, s), 2.88 (2H, q, J=7.3Hz), 3.30-3.45 (4H, m), 3.60-3.80 (3H, m), 3.80-3.90 (1H, m), 5.00-5.10 (1H, m), 7.10-7.30 (4H, m)

Reference Example 76

1-(Benzyloxycarbonyl)-3-(β-D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methylpyrazole

- 50 **[0154]** To a solution of 3-(β-D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methyl-1H-pyrazole (1.3g) in tetrahydrofuran (30mL) was added N-(benzyloxycarbonyloxy)-succinimide (1.6g), and the mixture was heated under reflux overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1-(benzyloxycarbonyl)-3-(β-D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-5-methylpyrazole (1.3g).
- 55 ¹H-NMR (CDCl₃) δ ppm:
1.27 (6H, d, J=6.3Hz), 2.35 (3H, s), 3.45-3.70 (6H, m), 3.76 (1H, dd, J=4.5, 12.0Hz), 3.85 (1H, dd, J=2.8, 12.0Hz), 4.40-4.50 (1H, m), 5.30-5.40 (2H, m), 5.48 (1H, d, J=8.0Hz), 6.70-6.80 (2H, m), 6.95-7.05 (2H, m), 7.25-7.50 (5H, m)

Reference Example 77

1-(Benzyloxycarbonyl)-3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole

[0155] To a solution of 1-(benzyloxycarbonyl)-3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole (0.20g) in 2,4,6-trimethylpyridine (4mL) was added ethyl chloroformate (0.092mL), and the mixture was stirred at room temperature for 1 day. To the reaction mixture were added water and citric acid monohydrate, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 1-(benzyloxy-carbonyl)-3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole (0.17g).

¹H-NMR (CD₃OD) δ ppm:

1.19 (3H, t, J=7.1Hz), 1.26 (6H, d, J=6.0Hz), 2.36 (3H, s), 3.30-3.50 (3H, m), 3.50-3.75 (3H, m), 4.10 (2H, q, J=7.1Hz), 4.25-4.35 (1H, m), 4.35-4.45 (1H, m), 4.45-4.60 (1H, m), 5.35-5.45 (2H, m), 5.45-5.60 (1H, m), 6.70-6.85 (2H, m), 7.00-7.15 (2H, m), 7.30-7.55 (5H, m)

Reference Example 78

1-(Benzyloxycarbonyl)-4-[(4-isopropoxyphenyl)methyl]-3-(6-*O*-methoxycarbonyl- β -D-glucopyranosyloxy)-5-methylpyrazole

[0156] The title compound was prepared in a similar manner to that described in Reference Example 77 using methyl chloroformate instead of ethyl chloroformate.

¹H-NMR (CDCl₃) δ ppm:

1.30 (6H, d, J=6.4Hz), 2.43 (3H, s), 3.45-3.70 (6H, m), 3.78 (3H, s), 4.39 (1H, dd, J=2.2, 11.8Hz), 4.40-4.55 (2H, m), 5.38 (2H, s), 5.40-5.50 (1H, m), 6.70-6.85 (2H, m), 7.00-7.10 (2H, m), 7.30-7.50 (5H, m)

Example 1

3-(6-*O*-Ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

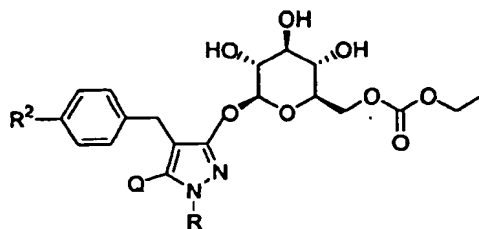
[0157] To a solution of 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole (0.10g) in 2,4,6-trimethylpyridine (1mL) was added ethyl chloroformate (0.072g), and the mixture was stirred at room temperature overnight. To the reaction mixture were added citric acid monohydrate (3.3g) and water, and the resulting mixture was purified by ODS solid phase extraction (washing solvent: distilled water, eluent: methanol). Further purification by column chromatography on silica gel (eluent: dichloromethane/ methanol = 10/1) and recrystallization (recrystallization solvent: ethyl acetate/hexane = 1/3) afforded 3-(6-*O*-ethoxy-carbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-1-isopropyl-5-methylpyrazole (0.084g).

¹H-NMR (CD₃OD) δ ppm:

1.23 (3H, t, J=7.0Hz), 1.26 (6H, d, J=5.8Hz), 1.30-1.40 (6H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 4.12 (2H, q, J=7.0Hz), 4.21 (1H, dd, J=5.4, 11.6Hz), 4.34 (1H, dd, J=1.7, 11.6Hz), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Examples 2-14

[0158] The compounds listed in Table 1 were prepared from the corresponding starting material in a similar manner to that described in Example 1.



[Table 1]

Example	R	R ²	Q
2	Methyl	Methoxy	Methyl
3	Methyl	Methylthio	Trifluoromethyl
4	Ethyl	Methylthio	Trifluoromethyl
5	Propyl	Methylthio	Trifluoromethyl
6	Propyl	Isopropoxy	Methyl
7	Ethyl	Isopropoxy	Methyl
8	Ethyl	Methoxy	Methyl
9	Propyl	Methoxy	Methyl
10	Ethyl	Ethoxy	Methyl
11	Propyl	Ethoxy	Methyl
12	Ethyl	Ethyl	Methyl
13	Propyl	Ethyl	Methyl
14	Butyl	isopropoxy	Methyl

Example 15

4-[(4-Isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxy-carbonyl-β-D-glucopyranosyloxy)-5-methylpyrazole

[0159] The title compound was prepared in a similar manner to that described in Example 1 using methyl chloroformate instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

1.26 (6H, d, J=6.1Hz), 1.30-1.40 (6H, m), 2.07 (3H, s), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 3.71 (3H, s), 4.22 (1H, dd, J=5.2, 11.7Hz), 4.35 (1H, dd, J=2.1, 11.7Hz), 4.35-4.45 (1H, m), 4.45-4.60 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Example 16

3-(6-O-Isobutyloxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole

[0160] The title compound was prepared in a similar manner to that described in Example 1 using isobutyl chloroformate instead of ethyl chloroformate.

¹H-NMR (CD₃OD) δ ppm:

0.90 (6H, d, J=6.7Hz), 1.26 (6H, d, J=5.9Hz), 1.30-1.40 (6H, m), 1.80-2.00 (1H, m), 2.07 (3H, s), 3.25-3.50 (4H, m), 3.60-3.70 (2H, m), 3.80-3.90 (2H, m), 4.21 (1H, dd, J=5.2, 11.5Hz), 4.36 (1H, dd, J=1.8, 11.5Hz), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

Example 17

4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(6-*O*-propionyl- β -D-glucopyranosyloxy)pyrazole

- 5 [0161] To a solution of 3-(β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole (0.10g) in 2,4,6-trimethylpyridine (1mL) was added propionyl chloride (0.072g) at 0°C, and the mixture was stirred for 5 hours. To the reaction mixture were added citric acid monohydrate (3.3g) and water, and the resulting mixture was purified by ODS solid phase extraction (washing solvent: distilled water, eluent: methanol). Further purification by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) afforded 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(6-*O*-propionyl- β -D-glucopyranosyloxy)pyrazole (0.074g)
- 10 ¹H-NMR (CD₃OD) δ ppm:
 1.05 (3H, t, J=7.5Hz), 1.26 (6H, d, J=5.9Hz), 1.30-1.40 (6H, m), 2.07 (3H, s), 2.27 (2H, q, J=7.5Hz), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 4.18 (1H, dd, J=5.6, 11.8Hz), 4.30 (1H, dd, J=2.2, 11.8Hz), 4.35-4.45 (1H, m), 4.45-4.55 (1H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)

15

Example 18

3-(6-*O*-Acetyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxy-phenyl)methyl]-1-isopropyl-5-methylpyrazole

- 20 [0162] The title compound was prepared in a similar manner to that described in Example 17 using acetyl chloride instead of propionyl chloride.
- ¹H-NMR (CD₃OD) δ ppm:
 1.26 (6H, d, J=6.4Hz), 1.30-1.40 (6H, m), 1.98 (3H, s), 2.08 (3H, s), 3.25-3.45 (4H, m), 3.60-3.70 (2H, m), 4.16 (1H, dd, J=5.6, 11.8Hz), 4.29 (1H, dd, J=2.0, 11.8Hz), 4.35-4.55 (2H, m), 5.00-5.10 (1H, m), 6.70-7.80(2H, m), 7.00-7.10 (2H, m)
- 25

Example 19

3-(6-*O*-Butyryl- β -D-glucopyranosyloxy)-4-[(4-isopropoxy-phenyl)methyl]-1-isopropyl-5-methylpyrazole

- 30 [0163] The title compound was prepared in a similar manner to that described in Example 17 using butyryl chloride instead of propionyl chloride.
- ¹H-NMR (CD₃OD) δ ppm:
 0.88 (3H, t, J=7.4Hz), 1.26 (6H, d, J=6.0Hz), 1.30-1.40 (6H, m), 1.50-1.65 (2H, m), 2.07 (3H, s), 2.15-2.30 (2H, m), 3.25-3.50 (4H, m), 3.60-3.70 (2H, m), 4.17 (1H, dd, J=5.7, 11.9Hz), 4.31 (1H, dd, J=2.0, 11.9Hz), 4.30-4.55 (2H, m), 5.00-5.10 (1H, m), 6.70-6.80 (2H, m), 7.00-7.10 (2H, m)
- 35

Example 20

- 40 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methyl-3-(6-*O*-pivaloyl- β -D-glucopyranosyloxy)pyrazole

- [0164] The title compound was prepared in a similar manner to that described in Example 17 using pivaloyl chloride instead of propionyl chloride.
- ¹H-NMR (CD₃OD) δ ppm:
 1.10 (9H, s), 1.26 (6H, d, J=6.1Hz), 1.30-1.40 (6H, m), 2.06 (3H, s), 3.30-3.45 (4H, m), 3.60-3.70 (2H, m), 4.16 (1H, dd, J=5.8, 11.7Hz), 4.30 (1H, dd, J=2.0, 11.7Hz), 4.30-4.55 (2H, m), 5.05-5.15 (1H, m), 6.70-6.80(2H, m), 7.00-7.10 (2H, m)
- 45

Example 21

- 50 1-Ethoxycarbonyl-3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyl-oxy)-4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole

- [0165] To a solution of 4-[(4-ethylthiophenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1H-pyrazole (0.03g) in 2,4,6-trimethylpyridine (0.5mL) was added ethyl chloroformate (0.021mL), and the mixture was stirred at room temperature overnight. To the reaction mixture was added 10% aqueous citric acid solution, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel (eluent: dichloromethane/ methanol = 10/1) to give 1-ethoxycarbonyl-3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyl-oxy)-
- 55

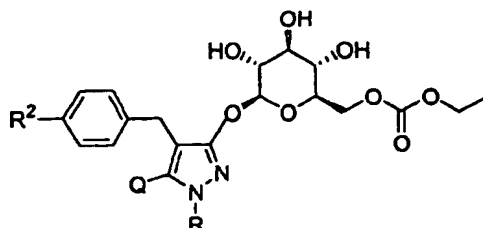
4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole (0.023g).

¹H-NMR (CD₃OD) δ ppm:

1.15-1.30 (6H, m), 1.39 (3H, t, J=7.1Hz), 2.37 (3H, s), 2.87 (2H, q, J=7.3Hz), 3.35-3.50 (3H, m), 3.60-3.80 (3H, m), 4.12 (2H, q, J=7.1Hz), 4.29 (1H, dd, J=5.3, 11.9Hz), 4.35-4.50 (3H, m), 5.50-5.60 (1H, m), 7.10-7.25 (4H, m)

Examples 22-43

[0166] The compounds listed in Table 2 were prepared from the corresponding starting material in a similar manner to that described in Example 21.



[Table 2]

Example	R	R ²	Q
22	Ethoxycarbonyl	Isopropoxy	Methyl
23	Ethoxycarbonyl	Propyl	Methyl
24	Ethoxycarbonyl	Isobutyl	Methyl
25	Ethoxycarbonyl	Propoxy	Methyl
26	Ethoxycarbonyl	Ethoxy	Methyl
27	Ethoxycarbonyl	Trifluoromethyl	Methyl
28	Ethoxycarbonyl	<i>tert</i> -Butyl	Methyl
29	Ethoxycarbonyl	Butoxy	Methyl
30	Ethoxycarbonyl	Methylthio	Methyl
31	Ethoxycarbonyl	Methylthio	Ethyl
32	Ethoxycarbonyl	Isopropyl	Methyl
33	Ethoxycarbonyl	Methylthio	Trifluoromethyl
34	Ethoxycarbonyl	Hydrogen	Trifluoromethyl
35	Ethoxycarbonyl	Methoxy	Trifluoromethyl
36	Ethoxycarbonyl	Methoxy	Methyl
37	Ethoxycarbonyl	Hydrogen	Methyl
38	Ethoxycarbonyl	Methyl	Methyl
39	Ethoxycarbonyl	Ethyl	Methyl
40	Ethoxycarbonyl	Methyl	Trifluoromethyl
41	Ethoxycarbonyl	Ethyl	Trifluoromethyl
42	Ethoxycarbonyl	Isopropyl	Trifluoromethyl
43	Ethoxycarbonyl	Chlorine	Trifluoromethyl

Example 44

3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-1-(ethoxy-carbonyloxymethyl)-4-[(4-methylthiophenyl)methyl]-5-methyl-pyrazole

5

[0167] To a solution of 3-(β -D-glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]-1*H*-pyrazole (0.11g) in water (0.5mL) and ethanol (0.1mL) was added formaldehyde (37% aqueous solution, 0.068mL), and the mixture was stirred at 40°C for 3 days. To the reaction mixture were added tetrahydrofuran and anhydrous magnesium sulfate, and the resulting insoluble material was removed by filtration. The solvent of the filtrate was removed under reduced pressure. The residue was dissolved in 2,4,6-trimethylpyridine (1mL). Ethyl chloroformate (0.099g) was added to the solution, and the mixture was stirred at room temperature overnight. To the reaction mixture were added citric acid monohydrate (4g) and water, and the resulting mixture was purified by ODS solid phase extraction (washing solvent: 10% aqueous citric acid solution, distilled water, eluent: methanol). Further purification by column chromatography on silica gel (eluent: dichloromethane/methanol = 15/1) afforded 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyl-oxy)-1-(ethoxycarbonyloxymethyl)-4-[(4-methylthiophenyl)-methyl]-5-methylpyrazole (0.058g).

15

¹H-NMR (CD₃OD) δ ppm:

1.23 (3H, t, J=7.1Hz), 1.26 (3H, t, J=7.1Hz), 2.18 (3H, s), 2.42 (3H, s), 3.30-3.45 (3H, m), 3.50-3.60 (1H, m), 3.63 (1H, d, J=16.0Hz), 3.70 (1H, d, J=16.0Hz), 4.13 (2H, q, J=7.1Hz), 4.18 (2H, q, J=7.1Hz), 4.28 (1H, dd, J=4.8, 11.7Hz), 4.39 (1H, dd, J=2.0, 11.7Hz), 5.25-5.35 (1H, m), 5.80-5.95 (2H, m), 7.10-7.20 (4H, m)

20

Example 45

1-Acetyl-4-[(4-ethylthiophenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methylpyrazole

25

[0168] To a solution of 4-[(4-ethylthiophenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methyl-1*H*-pyrazole (0.41g) in tetrahydrofuran (10mL) were added acetic acid (0.11mL) and acetic anhydride (0.18mL), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and diethyl ether was added to the residue. The resulting precipitated crystal was collected by filtration to give 1-acetyl-4-[(4-ethylthiophenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methylpyrazole (0.36g).

30

¹H-NMR (CD₃OD) δ ppm:

1.24 (3H, t, J=7.3Hz), 2.43 (3H, s), 2.54 (3H, s), 2.89 (2H, q, J=7.3Hz), 3.30-3.50 (4H, m), 3.60-3.75 (3H, m), 3.80-3.90 (1H, m), 5.45-5.55 (1H, m), 7.10-7.30 (4H, m)

Example 46

35

1-Acetyl-3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole

40

[0169] To a solution of 1-acetyl-4-[(4-ethylthiophenyl)methyl]-3-(β -D-glucopyranosyloxy)-5-methylpyrazole (0.03g) in 2,4,6-trimethylpyridine (0.5mL) was added ethyl chloroformate (0.012mL), and the mixture was stirred at room temperature overnight. To the reaction mixture was added 10% aqueous citric acid solution (5mL), and the resulting mixture was stirred at room temperature overnight. The resulting precipitates were collected by filtration and washed with 10% aqueous citric acid solution and water to give 1-acetyl-3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-ethylthiophenyl)methyl]-5-methylpyrazole (0.020g).

¹H-NMR (CD₃OD) δ ppm:

45

1.20 (3H, t, J=7.2Hz), 1.24 (3H, t, J=7.4Hz), 2.41 (3H, s), 2.55 (3H, s), 2.88 (2H, q, J=7.4Hz), 3.30-3.40 (1H, m), 3.40-3.50 (2H, m), 3.50-3.65 (1H, m), 3.65 (1H, d, J=15.8Hz), 3.72 (1H, d, J=15.8Hz), 4.05-4.15 (2H, m), 4.27 (1H, dd, J=6.3, 11.7Hz), 4.42 (1H, dd, J=2.0, 11.7Hz), 5.40-5.55 (1H, m), 7.10-7.30 (4H, m)

Example 47

50

3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methyl-1*H*-pyrazole

55

[0170] To a solution of 1-(benzyloxycarbonyl)-3-(6-*O*-ethoxy-carbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)-methyl]-5-methylpyrazole (0.17g) in tetrahydrofuran (4mL) was added 10% palladium-carbon powder, and the mixture was stirred under hydrogen atmosphere at room temperature for 3 hours. The resulting insoluble material was removed by filtration, and the solvent of the filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: dichloromethane/methanol = 10/1) to give 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxy-phenyl)methyl]-5-methyl-1*H*-pyrazole (0.10g).

¹H-NMR (CD₃OD) δ ppm:

1.23 (3H, t, J=7.1Hz), 1.26 (6H, d, J=6.0Hz), 2.04 (3H, s), 3.30-3.55 (4H, m), 3.61 (1H, d, J=15.9Hz), 3.67 (1H, d, J=15.9Hz), 4.12 (2H, q, J=7.1Hz), 4.27 (1H, dd, J=4.9, 11.7Hz), 4.38 (1H, dd, J=2.0, 11.7Hz), 4.45-4.60 (1H, m), 5.10-5.20 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

5

Example 48

4-[(4-isopropoxyphenyl)methyl]-3-(6-O-methoxycarbonyl-β-D-glucopyranosyloxy)-5-methyl-1H-pyrazole

10 **[0171]** The title compound was prepared in a similar manner to that described in Example 47 using 1-(benzyloxycarbonyl)-4-[(4-isopropoxyphenyl)methyl]-3-(6-O-methoxycarbonyl-β-D-glucopyranosyloxy)-5-methylpyrazole instead of 1-(benzyl-oxycarbonyl)-3-(6-O-ethoxycarbonyl-β-D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-5-methylpyrazole.

¹H-NMR (CD₃OD) δ ppm:

15 1.26 (6H, d, J=5.9Hz), 2.04 (3H, s), 3.30-3.55 (4H, m), 3.61 (1H, d, J=15.9Hz), 3.67 (1H, d, J=15.9Hz), 3.72 (3H, s), 4.28 (1H, dd, J=5.2, 11.7Hz), 4.39 (1H, dd, J=1.8, 11.7Hz), 4.45-4.55 (1H, m), 5.05-5.15 (1H, m), 6.70-6.80 (2H, m), 7.00-7.15 (2H, m)

Test Example 1

20

Assay for inhibitory effect on human SGLT2 activity

1) Construction of the plasmid vector expressing human SGLT2

25 **[0172]** Preparation of the cDNA library for PCR amplification was performed by reverse transcription of a total RNA deprived from human kidney (Ori gene) with oligo dT as the primer, using SUPERScript Preamplification System (Gibco-BRL: LIFE TECHNOLOGIES). The DNA fragment coding for human SGLT2 was amplified by the PCR reaction, in which the human kidney cDNA library described above was used as the template and the following oligo nucleotides 0702F and 0712R, presented as sequence number 1 and 2 respectively, were used as the primers. The amplified DNA
30 fragment was ligated into pCR-Blunt (Invitrogen), a vector for cloning, according to standard method of the kit. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformants was performed on the LB agar medium containing 50 µg/mL of kanamycin. After plasmid DNA was extracted and purified from the one of the transformants, amplifying of the DNA fragment coding for human SGLT2 was performed by the PCR reaction, in which the following oligo nucleotides 0714F and 0715R, presented as sequence number 3 and 4 respectively, were used as the primers. The amplified DNA fragment was digested with restriction enzymes, Xho I and Hind III, and then purified with Wizard Purification System (Promega). This purified DNA fragment was inserted at into the corresponding restriction sites of pcDNA3.1 (-) Myc/His - B (Invitrogen), a vector for expressing of fusion protein. The *Escherichia coli* HB101 was transformed according to usual method and then selection of the transformant was performed on the LB agar medium containing 100 µg/mL of ampicillin. After plasmid DNA was extracted and purified from
40 this transformant, the base sequence of the DNA fragment inserted at the multi-cloning sites of the vector pcDNA3.1 (-) Myc/His - B was analyzed. This clone had a single base substitution (ATC which codes for the isoleucine-433 was substituted by GTC) compared with the human SGLT2 reported by Wells *et al* (Am. J. Physiol., Vol. 263, pp. 459-465 (1992)). Sequentially, a clone in which valine is substituted for isoleucine-433 was obtained. This plasmid vector expressing human SGLT2 in which the peptide presented as sequence number 5 is fused to the carboxyl terminal alanine
45 residue was designated KL29.

Sequence Number 1 ATGGAGGAGCACACAGAGGC

50

Sequence Number 2 GGCATAGAAGCCCCAGAGGA

Sequence Number 3 AACCTCGAGATGGAGGAGCACACAGAGGC

55

Sequence Number 4 AACAAAGCTTGGCATAGAAGCCCCAGAGGA

Sequence Number 5 KLGPEQKLISEEDLNSAVDHHHHHH

5 2) Preparation of the cells expressing transiently human SGLT2

[0173] KL29, the plasmid coding human SGLT2, was transfected into COS-7 cells (RIKEN CELL BANK RCB0539) by electroporation. Electroporation was performed with GENE PULSER II (Bio-Rad Laboratories) under the condition: 0.290 kV, 975 μ F, 2×10^6 cells of COS-7 cell and 20 μ g of KL29 in 500 μ L of OPTI-MEM I medium (Gibco-BRL: LIFE TECHNOLOGIES) in the 0.4 cm type cuvette. After the gene transfer, the cells were harvested by centrifugation and resuspended with OPTI-MEM I medium (1mL/cuvette). To each well in 96-wells plate, 125 μ L of this cell suspension was added. After overnight culture at 37 °C under 5 % CO₂, 125 μ L of DMEM medium which is containing 10 % of fetal bovine serum (Sanko Jyunyaku), 100 units/mL sodium penicillin G (Gibco-BRL: LIFE TECHNOLOGIES), 100 μ g/mL streptomycin sulfate (Gibco-BRL: LIFE TECHNOLOGIES) was added to each well. These cells were cultured until the next day and then they were used for the measurement of the inhibitory activity against the uptake of methyl- α -D-glucopyranoside.

3) Measurement of the inhibitory activity against the uptake of methyl- α -D-glucopyranoside

[0174] After a test compounds was dissolved in dimethyl sulfoxide and diluted with the uptake buffer (a pH 7.4 buffer containing 140 mM sodium chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 5 mM methyl- α -D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid and 5 mM tris (hydroxymethyl) aminomethane), each diluent was used as test sample for measurement of the inhibitory activity. After removal of the medium of the COS-7 cells expressing transiently human SGLT2, to each well 200 μ L of the pretreatment buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl] ethane sulfonic acid and 5 mM tris (hydroxymethyl)-aminomethane) was added, and the cells were incubated at 37 °C for 10 minutes. After the pretreatment buffer was removed, 200 μ L of the same buffer was added again, and the cells were incubated at 37 °C for 10 minutes. The buffer for measurement was prepared by adding of 7 μ L of methyl- α -D- (U-14C)glucopyranoside (Amersham Pharmacia Biotech) to 525 μ L of the prepared test sample. For the control, the buffer for measurement without test compound was prepared. For the estimate of the basal uptake in the absence of test compound and sodium, the buffer for measurement of the basal uptake, which contains 140 mM choline chloride in place of sodium chloride, was prepared similarly. After the pretreatment buffer was removed, 75 μ L of each buffer for measurement was added to each well, the cells were incubated at 37 °C for 2 hours. After the buffer for measurement was removed, 200 μ L of the washing buffer (a pH 7.4 buffer containing 140 mM choline chloride, 2 mM potassium chloride, 1 mM calcium chloride, 1 mM magnesium chloride, 10 mM methyl- α -D-glucopyranoside, 10 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl] ethane sulfonic acid and 5 mM tris(hydroxymethyl)aminomethane) was added to each well and immediately removed. After two additional washing, the cells were solubilized by addition of 75 μ L of 0.2 mol/L sodium hydroxide to each well. After the cell lysates were transferred to the PicoPlate (Packard) and 150 μ L of MicroScint-40 (Packard) was added to each well, the radioactivity was measured with microplate scintillation counter TopCount (Packard). The difference in uptake was obtained as 100 % value by subtracting the radioactivity in the basal uptake from that in control and then the concentrations at which 50 % of uptake were inhibited (IC₅₀) were calculated from the concentration-inhibition curve by least square method. The results are shown in the following Table 3.

[Table 3]

Test compound	IC ₅₀ value (nM)
Reference Example 37	181
Reference Example 38	441
Reference Example 39	346
Reference Example 40	702
Reference Example 41	185
Reference Example 45	84
Reference Example 46	509

[Table 3] (continued)

Test compound	IC ₅₀ value (nM)
Reference Example 47	441
Reference Example 48	679
Reference Example 50	415
Reference Example 51	383
Reference Example 54	835
Reference Example 57	280
Reference Example 58	190
Reference Example 60	634
Reference Example 72	369
WAY-123783	>100000

Test Example 2

Assay for oral absorbability

1) Preparation of the samples for measurement of the drug concentration after intravenous injection to the tail vein

[0175] As experimental animal, overnight fasted SD rats (CLEA JAPAN, INC., male, 5 weeks of age, 140-170g) were used. Sixty mg of a test compound was dissolved by adding of 1.8 mL of ethanol, 7.2 mL of polyethylene glycol 400 and 9 mL of saline, and then 3.3 mg/mL solution was prepared. The body weights of rats were measured and the solution of the test compound was intravenously injected to the tail vein of unanesthetized rats at the dose of 3 mL/kg (10 mg/kg). The intravenous injection to the tail was performed with 26 G injection needle and 1 mL syringe. The sampling times for collection of blood were 2, 5, 10, 20, 30, 60 and 120 minutes after the intravenous injection to the tail. The blood was centrifuged and the plasma was used as the sample for measurement of the drug concentration in plasma.

2) Preparation of the samples for measurement of the drug concentration after oral administration

[0176] As experimental animal, overnight fasted SD rats (CLEA JAPAN, INC., male, 5 weeks of age, 140-170g) were used. A test compound was suspended or dissolved in 0.5 % sodium carboxymethylcellulose solution at the concentration of 1 mg/mL of active form. When a homogenous suspension was not obtained under these conditions, the test compound was dissolved in ethanol at the concentration of 100 mg/mL of active form and then suspension was obtained by adding this solution to 99 times volumes of 0.5 % sodium carboxymethylcellulose solution. After the body weights of rats were measured, the liquid containing the test compound described above was orally administered at the dose of 10 mL/kg (10 mg/kg as active form). The oral administration was performed with gastric tube for rat and 2.5 mL syringe. The sampling times for collection of blood were 15, 30, 60, 120 and 240 minutes after the oral administration. The blood was centrifuged and the plasma was used as the sample for measurement of the drug concentration in plasma.

3) Measurement of drug concentration

Method A

[0177] To 0.1 mL of the plasma obtained in 1) and 2) described above, an adequate amount of an adequate internal standard material was added according to the usual method and then deproteinization was performed by adding of 1 mL of methanol. After centrifugation, the methanol phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 300 μ L of the mobile phase and 30 μ L aliquot of the solution was injected into HPLC. The drug concentration in plasma was measured by HPLC method under the condition as follows. To 0.1 mL of the blank plasma an adequate internal standard and various concentrations of corresponding active form of the compound were suitably added according to the usual method, similar operating procedures described above were followed and then

the standard curve was prepared.

Column: Develosil ODS-UG-5 (4.6 x 250 mm)
 Mobile phase: acetonitrile / 10 mM phosphate buffer (pH 3.0) = 22: 78 (v/v)
 Column temperature: 50 °C
 Flow rate: 1.0 mL/minute
 Wavelength for measurement: UV 232 nm

Method B

[0178] To 50 µL of the plasma obtained in 1) and 2) described above, an adequate amount of an adequate internal standard material was added according to usual method and 100 µL of distilled water was added, and then extraction was performed by adding of 1 mL of diethyl ether. After centrifugation, the diethyl ether phase was evaporated to dryness under a stream of nitrogen. The residue was dissolved in 200 µL of the mobile phase and 10 µL aliquot of the solution was injected into LC-MS/MS. The drug concentration in plasma was measured by LC-MS/MS method under the conditions as follows. To 50 µL of the blank plasma an adequate internal standard and various concentrations of corresponding active form of compound were suitably added according to the usual method, similar operating procedures described above were followed and then the standard curve was prepared

LC

Column: Symmetry C₈ (2.1 x 20 mm)
 Mobile phase: acetonitrile / 0.1 % acetic acid solution = 65: 35 (v/v)
 Column temperature: 40 °C
 Flow rate: 0.2 mL/minute

MS/MS

Ionization method: ESI (Turbo Ion Spray) , positive ion detection mode
 Ion spray voltage: 5000 V
 Heater gas temperature: 450 °C
 Collision energy: 17.5 V
 Multiplier voltage: 2300 V
 Flow rate of turbo ion spray gas: 7000 mL/min
 Nebulizer gas: 11 BIT
 Curtain gas: 11 BIT
 Collision gas: 4 BIT

[0179] Each area under the plasma concentration-time curve by intravenous injection to the tail vein and oral administration of test compound was estimated with WinNonlin Standard made by Pharsight Corporation from the plasma concentrations at each time obtained from method A and B and then the bioavailability (%) was calculated based on the following formula. The results are shown in the following Table 4.

$$\text{Bioavailability(\%)} =$$

(Area under the Plasma Concentration - Time Curve by Oral

Administration/Area under the Plasma Concentration - Time Curve

by Intravenous Injection to the Tail Vein) x 100

[Table 4]

Test compound	Method	Bioavailability(%)
Example 1	B	27
Example 15	B	27
Example 16	B	32

[Table 4] (continued)

Test compound	Method	Bioavailability(%)
Example 47	A	15
Example 48	A	11
Reference Example 37	A	0

Test Example 3

Assay for the facilitatory effect on urinary glucose excretion

[0180] As experimental animal, overnight fasted SD rats (Japan SLC. Inc., male, 7 weeks of age, 202-221g) were used. A Test compound was suspended in 0.5 % sodium carboxymethylcellulose solution at the concentration of 2 mg/mL. When a homogenous suspension was not obtained under these conditions, the test compound was dissolved in ethanol at the concentration of 200 mg/mL of active form and then 2 mg/mL suspension was obtained by adding this solution to 99 times volumes of 0.5 % sodium carboxymethylcellulose solution. Apart of this suspension was diluted with 0.5 % sodium carboxymethylcellulose solution and then 0.6 and 0.2 mg/mL suspensions were prepared. After the body weights of rats were measured, the test suspension was orally administered at the dose of 5 mL/kg (1, 3 and 10 mg/kg). For control, only 0.5 % sodium carboxymethylcellulose solution was orally administered at the dose of 5 mL/kg. Immediately after this oral administration, 400 g/L glucose solution was orally administered at the dose of 5 mL/kg (2 g/kg). The oral administration was performed with gastric tube for rat and 2.5 mL syringe. The head count in one group was 3. Collection of urine was performed in metabolic cage after the glucose administration was finished. The sampling time for collection of urine was 24 hours after the glucose administration. After collection of urine was finished, the urine volume was recorded and the urinary glucose concentration was measured. The glucose concentration was measured with a kit for laboratory test: Glucose B-Test WAKO (Wako Pure Chemical Industries, Ltd.). The amount of urinary glucose excretion in 24 hours per 200 g of body weight was calculated from urine volume, urinary glucose concentration and body weight. The results are shown in the following Table 5.

[Table 5]

Test compound	Dose (mg/kg)	Amount of Urinary Glucose Excretion weight) (mg/24 hours-200g body weight)
Example 1	1	1.6
	3	28.3
	10	127.5
Example 15	1	1.7
	3	36.8
	10	167.3

Test Example 4

Acute toxicity test

[0181] After 4 week old male ICR mice (Japan SLC. Inc., 20 - 25 g, 5 animals in each group) were fasted for 4 hours, the suspension (200 mg/mL) prepared by adding of 0.5 % sodium carboxymethylcellulose solution to the test compound was orally administered at the dose of 10 mL/kg (2000 mg/kg). Observation was performed until 24 hours after the administration. The results are shown in the following Table 6.

[Table 6]

Test compound	Death number
Example 48	0 / 5

Industrial Applicability

5 [0182] The glucopyranosyloxypyrazole derivatives represented by the above general formula (I) of the present invention or pharmaceutically acceptable salts thereof have an improved oral absorption. In addition, they show an excellent hypoglycemic effect by excreting excess glucose into the urine through preventing the reabsorption of glucose at the kidney because they are converted into glucopyranosyloxypyrazole derivatives represented by the above general formula (II) as their active forms *in vivo* and exhibit a potent inhibitory activity in human SGLT2. Therefore, the present invention can provide agents for the prevention or treatment of a disease associated with hyperglycemia such as diabetes, diabetic complications, obesity or the like, which are also suitable as oral formulations.

10

[SEQUENCE LISTING FREE TEXT]

[0183] Sequence Number 1: Synthetic DNA primer
[0184] Sequence Number 2: Synthetic DNA primer
15 [0185] Sequence Number 3: Synthetic DNA primer
[0186] Sequence Number 4: Synthetic DNA primer
[0187] Sequence Number 5: Peptide fused to the carboxyl terminal alanine residue of human SGLT2

20

25

30

35

40

45

50

55

SEQUENCE LISTING

5 <110> KISSEI PHARMACEUTICAL CO., LTD.
FUJIKURA, Hideki
FUSHIMI, Nobuhiko
NISHIMURA, Toshihiro
NAKABAYASHI, Takeshi
10 ISAJI, Masayuki

<120> GLUCOPYRANOSYLOXYPYRAZOLE DERIVATIVES AND PHARMACEUTICAL USES THEREOF

<130> PCT-A0138

15 <150> JP 2000/403534
<151> 2000-12-28

<160> 5

<170> PatentIn version 3.0 and MS Word

20 <210> 1
<211> 20
<212> DNA
<213> Artificial Sequence

25 <220>
<223> Synthetic DNA primer

<400> 1
atggaggagc acacagaggc 20

30 <210> 2
<211> 20
<212> DNA
<213> Artificial Sequence

35 <220>
<223> Synthetic DNA primer

<400> 2
ggcatagaag cccagagga 20

40 <210> 3
<211> 29
<212> DNA
<213> Artificial Sequence

45 <220>
<223> Synthetic DNA primer

<400> 3
aacctcgaga tggaggagca cacagaggc 29

50 <210> 4
<211> 29
<212> DNA
<213> Artificial Sequence

55

<220>

<223> Synthetic DNA primer

5

<400> 4

aacaagcttg gcatagaagc cccagagga

29

10

<210> 5

<211> 25

<212> PRT

<213> Artificial Sequence

15

<220>

<223> Peptide fused to the carboxyl terminal
alanine residue of human SGLT2

<400> 5

20

Lys Leu Gly Pro Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Asn Ser
1 5 10 15

Ala Val Asp His His His His His His
20 25

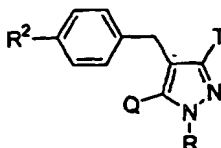
25

Claims

30

1. A glucopyranosyloxypyrazole derivative represented by the general formula:

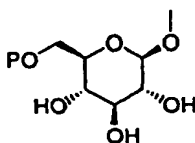
35



40

wherein R represents a hydrogen atom, a lower alkyl group or a group forming a prodrug; one of Q and T represents a group represented by the general formula:

45

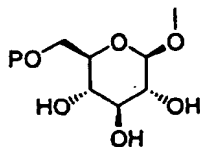


50

55

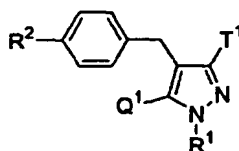
(wherein P represents a hydrogen atom or a group forming a prodrug) , while the other represents a lower alkyl group or a halo (lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo (lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

2. A glucopyranosyloxypyrazole derivative as claimed in claim 1 wherein T represents a group represented by the general formula:



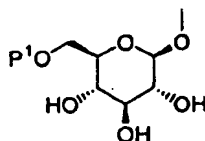
(wherein P represents a hydrogen atom or a group forming a prodrug); and Q represents a lower alkyl group or a halo(lower alkyl) group, or a pharmaceutically acceptable salt thereof.

3. A glucopyranosyloxypyrazole derivative as claimed in claim 1, represented by the general formula:



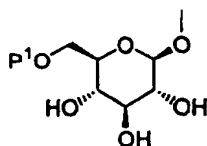
wherein R¹ represents a hydrogen atom, a lower alkyl group, a lower acyl group, a lower alkoxy-carbonyl group, a lower acyloxymethyl group or a lower alkoxy-carbonyloxymethyl group; one of Q¹ and T¹ represents a group represented by the general formula:

(wherein P¹ represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower



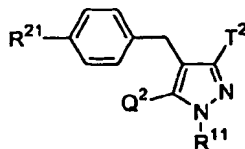
alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group), while the other represents a lower alkyl group or a halo(lower alkyl) group; R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, a halo(lower alkyl) group or a halogen atom; and with the proviso that P does not represent a hydrogen atom when R¹ represents a hydrogen atom or a lower alkyl group, or a pharmaceutically acceptable salt thereof.

4. A glucopyranosyloxypyrazole derivative as claimed in claim 3 wherein T¹ represents a group represented by the general formula:

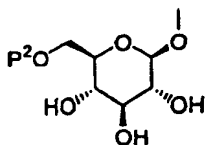


(wherein P¹ represents a hydrogen atom, a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group); and Q¹ represents a lower alkyl group or a halo (lower alkyl) group, or a pharmaceutically acceptable salt thereof.

5. A glucopyranosyloxypyrazole derivative as claimed in claim 3, represented by the general formula:

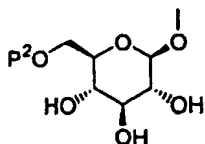


wherein R¹¹ represents a hydrogen atom or a lower alkyl group; one of Q² and T² represents a group represented by the general formula:



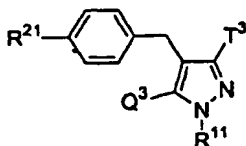
(wherein P² represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group or a lower alkoxy-substituted (lower alkoxycarbonyl) group), while the other represents a lower alkyl group; and R²¹ represents a lower alkyl group, a lower alkoxy group or a lower alkylthio group, or a pharmaceutically acceptable salt thereof.

6. A glucopyranosyloxypyrazole derivative as claimed in claim 5 wherein T² represents a group represented by the general formula:

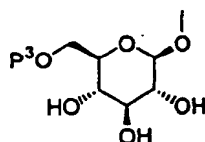


(wherein P² represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxycarbonyl-substituted (lower acyl) group, a lower alkoxycarbonyl group or a lower alkoxy-substituted (lower alkoxycarbonyl) group); and Q² represents a lower alkyl group, or a pharmaceutically acceptable salt thereof.

7. A glucopyranosyloxypyrazole derivative as claimed in claim 5, represented by the general formula:
wherein R¹¹ represents a hydrogen atom or a lower alkyl group;

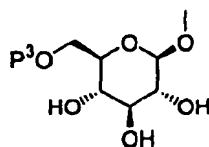


one of Q³ and T³ represents a group represented by the general formula:



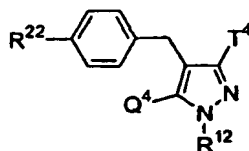
(wherein P³ represents a lower acyl group or a lower alkoxy-carbonyl group), while the other represents a lower alkyl group; and R²¹ represents a lower alkyl group, a lower alkoxy group or a lower alkylthio group, or a pharmaceutically acceptable salt thereof.

8. A glucopyranosyloxypyrazole derivative as claimed in claim 7 wherein T³ represents a group represented by the general formula:

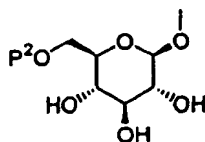


(wherein P³ represents a lower acyl group or a lower alkoxy-carbonyl group); and Q³ represents a lower alkyl group, or a pharmaceutically acceptable salt thereof.

9. A glucopyranosyloxypyrazole derivative as claimed in claim 5, represented by the general formula:

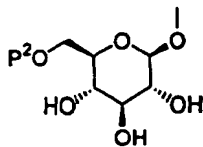


wherein R¹² represents a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms; one of Q⁴ and T⁴ represents a group represented by the general formula:



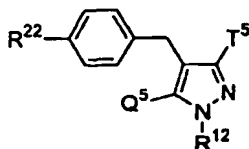
(wherein P² represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group), while the other represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms; and R²² represents a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

10. A glucopyranosyloxypyrazole derivative as claimed in claim 9 wherein T⁴ represents a group represented by the general formula:

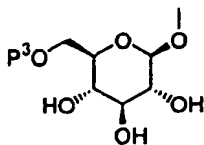


(wherein P^2 represents a lower acyl group, a lower alkoxy-substituted (lower acyl) group, a lower alkoxy-carbonyl-substituted (lower acyl) group, a lower alkoxy-carbonyl group or a lower alkoxy-substituted (lower alkoxy-carbonyl) group); and Q^4 represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

11. A glucopyranosyloxypyrazole derivative as claimed in claim 9, represented by the general formula:

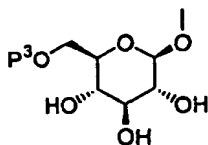


wherein R^{12} represents a hydrogen atom or a straight-chained or branched alkyl group having 1 to 3 carbon atoms; one of Q^5 and T^5 represents a group represented by the general formula:



(wherein P^3 represents a lower acyl group or a lower alkoxy-carbonyl group), while the other represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms; and R^{22} represents a straight-chained or branched alkyl group having 1 to 4 carbon atoms, a straight-chained or branched alkoxy group having 1 to 3 carbon atoms or a straight-chained or branched alkylthio group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

12. A glucopyranosyloxypyrazole derivative as claimed in claim 11 wherein T^5 represents a group represented by the general formula:



(wherein P^3 represents a lower acyl group or a lower alkoxy-carbonyl group); and Q^5 represents a straight-chained or branched alkyl group having 1 to 3 carbon atoms, or a pharmaceutically acceptable salt thereof.

13. A glucopyranosyloxypyrazole derivative as claimed in claim 12, which is selected from the group consisting of 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-O-methoxy-carbonyl- β -D-glucopyranosyloxy)-5-methylpyrazole, 3-(6-O-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole,

- 3-(6-*O*-isopropoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole, 3-(6-*O*-isobutoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole, 4-[(4-ethylphenyl)methyl]-1-isopropyl-3-(6-*O*-methoxy-carbonyl- β -D-glucopyranosyloxy)-5-methylpyrazole, 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-ethyl-phenyl)methyl]-1-isopropyl-5-methylpyrazole, 4-[(4-ethylphenyl)methyl]-3-(6-*O*-isopropoxycarbonyl- β -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole, 4-[(4-ethylphenyl)methyl]-3-(6-*O*-isobutoxycarbonyl- β -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole, 4-[(4-ethoxyphenyl)methyl]-1-isopropyl-3-(6-*O*-methoxy-carbonyl- β -D-glucopyranosyloxy)-5-methylpyrazole, 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-ethoxy-phenyl)methyl]-1-isopropyl-5-methylpyrazole, 4-[(4-ethoxyphenyl)methyl]-3-(6-*O*-isopropoxycarbonyl- β -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole, 4-[(4-ethoxyphenyl)methyl]-3-(6-*O*-isobutoxycarbonyl- β -D-glucopyranosyloxy)-1-isopropyl-5-methylpyrazole, 1-isopropyl-3-(6-*O*-methoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole, 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-1-isopropyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole, 3-(6-*O*-isopropoxycarbonyl- β -D-glucopyranosyloxy)-1-iso-propyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole, 3-(6-*O*-isobutoxycarbonyl- β -D-glucopyranosyloxy)-1-iso-propyl-4-[(4-methoxyphenyl)methyl]-5-methylpyrazole, 1-isopropyl-3-(6-*O*-methoxycarbonyl- β -D-glucopyranosyloxy)-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole, 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-1-isopropyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole, 3-(6-*O*-isopropoxycarbonyl- β -D-glucopyranosyloxy)-1-iso-propyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole and 3-(6-*O*-isobutoxycarbonyl- β -D-glucopyranosyloxy)-1-iso-propyl-5-methyl-4-[(4-methylthiophenyl)methyl]pyrazole.
14. A glucopyranosyloxy pyrazole derivative as claimed in claim 13, which is selected from the group consisting of 4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-3-(6-*O*-methoxy-carbonyl- β -D-glucopyranosyloxy)-5-methylpyrazole, 3-(6-*O*-ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole, 3-(6-*O*-isopropoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole and 3-(6-*O*-isobutoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-iso-propoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole.
15. 3-(6-*O*-Ethoxycarbonyl- β -D-glucopyranosyloxy)-4-[(4-isopropoxyphenyl)methyl]-1-isopropyl-5-methylpyrazole.
16. A pharmaceutical composition comprising as an active ingredient a glucopyranosyloxy pyrazole derivative as claimed in claim 1-15 or a pharmaceutically acceptable salt thereof.
17. A pharmaceutical composition as claimed in claim 16 wherein the composition is a human SGLT2 inhibitor.
18. A pharmaceutical composition as claimed in claim 16 or 17 wherein the composition is an agent for the prevention or treatment of a disease associated with hyperglycemia.
19. A pharmaceutical composition as claimed in claim 18 wherein the disease associated with hyperglycemia is selected from the group consisting of diabetes, diabetic complications, obesity, hyperinsulinemia, glucose metabolism disorder, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, lipid metabolism disorder, atherosclerosis, hypertension, congestive heart failure, edema, hyperuricemia and gout.
20. A pharmaceutical composition as claimed in claim 19 wherein the disease associated with hyperglycemia is diabetes.
21. A pharmaceutical composition as claimed in claim 19 wherein the disease associated with hyperglycemia is diabetic complications.
22. A pharmaceutical composition as claimed in claim 19 wherein the disease associated with hyperglycemia is obesity.
23. A pharmaceutical composition as claimed in claim 16-22 wherein the composition is an oral formulation.
24. A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of a glucopyranosyloxy pyrazole derivative as claimed in claim 1-15 or a pharmaceutically acceptable salt thereof.
25. A use of a glucopyranosyloxy pyrazole derivative as claimed in claim 1-15 or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

26. A pharmaceutical combination which comprises (A) a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinsitol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylidantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probcol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalinizer.
27. A pharmaceutical combination claimed in claim 26 for the prevention or treatment of a disease associated with hyperglycemia.
28. A pharmaceutical combination claimed in claim 27 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist and an appetite suppressant, and the disease associated with hyperglycemia is diabetes.
29. A pharmaceutical combination claimed in claim 28 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue and an amylin agonist.
30. A pharmaceutical combination claimed in claim 29 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer and an insulin preparation.
31. A pharmaceutical combination claimed in claim 27 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, a biguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B

- inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, glycogen synthase kinase-3 inhibitors, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproduct formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipidperoxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimo-clomol, sulodexide, Y-128, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist and a diuretic agent, and the disease associated with hyperglycemia is diabetic complications.
32. A pharmaceutical combination claimed in claim 31 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an aldose reductase inhibitor, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor and an angiotensin II receptor antagonist.
33. A pharmaceutical combination claimed in claim 27 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, a β_3 -adrenoceptor agonist and an appetite suppressant, and the disease associated with hyperglycemia is obesity.
34. A pharmaceutical combination claimed in claim 33 wherein the active ingredient other than a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof is at least one member selected from the group consisting of a β_3 -adrenoceptor agonist and an appetite suppressant.
35. A pharmaceutical combination claimed in claim 34 wherein the appetite suppressant is a drug selected from the group consisting of a monoamine reuptake inhibitor, a serotonin reuptake inhibitor, a serotonin releasing stimulant, a serotonin agonist, a noradrenaline reuptake inhibitor, a noradrenaline releasing stimulant, an α_1 -adrenoceptor agonist, a β_2 -adrenoceptor agonist, a dopamine agonist, a cannabinoid receptor antagonist, a γ -aminobutyric acid receptor antagonist, a H_3 -histamine antagonist, L-histidine, leptin, a leptin analogue, a leptin receptor agonist, a melanocortin receptor agonist, α -melanocyte stimulating hormone, cocaine-and amphetamine-regulated transcript, mahogany protein, an enterostatin agonist, calcitonin, calcitonin-gene-related peptide, bombesin, a cholecystokinin agonist, oricotropin-releasing hormone, a corticotropin-releasing hormone analogue, a corticotropin-releasing hormone agonist, urocortin, somatostatin, a somatostatin analogue, a somatostatin receptor agonist, pituitary adenylate cyclase-activating peptide, brain-derived neurotrophic factor, ciliary neurotrophic factor, thyrotropin-releasing hormone, neurotensin, sauvagine, a neuropeptide Y antagonist, an opioid peptide antagonist, a galanin antagonist, a melanin-concentrating hormone antagonist, an agouti-related protein inhibitor and an orexin receptor antagonist.
36. A method for the prevention or treatment of a disease associated with hyperglycemia, which comprises administering an effective amount of (A) a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof, in combination with (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylin agonist, an aldose reductase inhibitor, an advanced glycation endproduct formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-

derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probucol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer.

37. A use of (A) a glucopyranosyloxypyrazole derivative claimed in claim 1-15 or a pharmaceutically acceptable salt thereof, and (B) at least one member selected from the group consisting of an insulin sensitivity enhancer, a glucose absorption inhibitor, abiguanide, an insulin secretion enhancer, an insulin preparation, a glucagon receptor antagonist, an insulin receptor kinase stimulant, a tripeptidyl peptidase II inhibitor, a dipeptidyl peptidase IV inhibitor, a protein tyrosine phosphatase-1B inhibitor, a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a fructose-bisphosphatase inhibitor, a pyruvate dehydrogenase inhibitor, a hepatic gluconeogenesis inhibitor, D-chiroinositol, a glycogen synthase kinase-3 inhibitor, glucagon-like peptide-1, a glucagon-like peptide-1 analogue, a glucagon-like peptide-1 agonist, amylin, an amylin analogue, an amylinagonist, an aldose reductase inhibitor, an advanced glycation endproducts formation inhibitor, a protein kinase C inhibitor, a γ -aminobutyric acid receptor antagonist, a sodium channel antagonist, a transcript factor NF- κ B inhibitor, a lipid peroxidase inhibitor, an *N*-acetylated- α -linked-acid-dipeptidase inhibitor, insulin-like growth factor-I, platelet-derived growth factor, a platelet-derived growth factor analogue, epidermal growth factor, nerve growth factor, a carnitine derivative, uridine, 5-hydroxy-1-methylhydantoin, EGB-761, bimoclomol, sulodexide, Y-128, a hydroxymethyl-glutaryl coenzyme A reductase inhibitor, a fibric acid derivative, a β_3 -adrenoceptor agonist, an acyl-coenzyme A cholesterol acyltransferase inhibitor, probucol, a thyroid hormone receptor agonist, a cholesterol absorption inhibitor, a lipase inhibitor, a microsomal triglyceride transfer protein inhibitor, a lipoxygenase inhibitor, a carnitine palmitoyl-transferase inhibitor, a squalene synthase inhibitor, a low-density lipoprotein receptor enhancer, a nicotinic acid derivative, a bile acid sequestrant, a sodium/bile acid cotransporter inhibitor, a cholesterol ester transfer protein inhibitor, an appetite suppressant, an angiotensin-converting enzyme inhibitor, a neutral endopeptidase inhibitor, an angiotensin II receptor antagonist, an endothelin-converting enzyme inhibitor, an endothelin receptor antagonist, a diuretic agent, a calcium antagonist, a vasodilating antihypertensive agent, a sympathetic blocking agent, a centrally acting antihypertensive agent, an α_2 -adrenoceptor agonist, an antiplatelets agent, a uric acid synthesis inhibitor, a uricosuric agent and a urinary alkalizer, for the manufacture of a pharmaceutical composition for the prevention or treatment of a disease associated with hyperglycemia.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11348

A. CLASSIFICATION OF SUBJECT MATTER Int.Cl ⁷ C07H17/02, A61K31/7056, A61P43/00, 3/10, 3/04, 3/06, 9/10, 9/12, 9/04, 19/06, 7/10 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) Int.Cl ⁷ C07H17/02, A61K31/7056, A61P43/00, 3/10, 3/04, 3/06, 9/10, 9/12, 9/04, 19/06, 7/10 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) REGISTRY (STN), CAPLUS (STN), CAOLD (STN)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO, 01/16147, A1 (Kissei Pharmaceutical Co., Ltd.), 08 March, 2001 (08.03.01), (Family: none)	1-23, 25-35, 37
A	KENNETH L. KEES, et al., New Potent Antihyperglycemic Agents in db/db Mice: Synthesis and Structure-Activity Relationship Studies of (4-Substitutedbenzyl) (trifluoromethyl)pyrazoles and -pyrazolones, J.Med.Chem., 1996, Vol.39, No.20, pages 3920 to 3928	1-23, 25-35, 37
A	US, 5264451, A (American Home Products Corp.), 23 November, 1993 (23.11.93), & US 5274111 A	1-23, 25-35, 37
A	JP, 4-234851, A (Laboratoire U.P.S.A), 24 August, 1992 (24.08.92), & EP 449699 A2 & FR 2659655 A1 & ZA 9101925 A & AU 9173591 A1 & CA 2038428 A	1-23, 25-35, 37
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
Date of the actual completion of the international search 25 March, 2002 (25.03.02)		Date of mailing of the international search report 09 April, 2002 (09.04.02)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.		Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11348

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP, 598359, A1 (Tanabe Seiyaku Co., Ltd.), 25 May, 1994 (25.05.94), & JP 2906978 B2 & CA 2102591 A & US 5424406 A & TW 283643 A & US 5731292 A & SG 54120 A1 & DE 69328856 B & ES 2149186 T3 & KR 211438 B1	1-23, 25-35, 37

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP01/11348

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.: 24, 36
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 24 and 36 pertain to methods for treatment of the human body by therapy.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)